CARBON–CARBON BOND-FORMING REACTIONS: INSERTION, OLEFINATION AND NUCLEOPHILIC SUBSTITUTION OF HYDROGEN IN ARENES

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
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To my daughter Oana Daniela and my son Andrei with love

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Chairman: Alan R. Katritzky, FRS
Major Department: Chemistry

1-Arylmethylbenzotriazoles, 1-methoxymethylbenzotriazole and 1-(diarylmethyl) benzotriazoles are excellent carbon-carbon bond forming reagents where benzotriazole acts as both an activator to proton loss and as a leaving group.

Anions formed from the lithiation of a variety of 1-arylmethyl- and 1-heteroarylmethyl-benzotriazoles undergo addition to aliphatic and aromatic aldehydes, and cyclic and acyclic ketones. Subsequent *in situ* thermal rearrangements of the intermediates in the presence of zinc bromide provided a wide variety of one-carbon chain-extended or ring-expanded α-aryl- and α-heteroaryl substituted ketones in moderate to excellent yields with excellent regioselectivity in most cases. Substituent effects on the relative migration rates were investigated in the insertion reactions of 1-(4-methoxybenzyl)benzotriazole with benzophenones. The small and negative Hammett ρ^+ value (-0.92) suggests that the rearrangements proceed *via* early, reagent-like, electron deficient transition states.

Peterson olefination of aldehydes and ketones with the trimethylsilyl(methoxy)(benzotriazol-1-yl)methyl anion afforded 1-(benzotriazol-1-yl)-1-methoxy-1-alkenes which were treated without isolation with zinc bromide and hydrochloric acid, to yield the corresponding one-carbon homologated carboxylic acids in good overall yields.

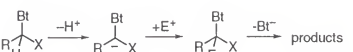
The vicinal elimination of silicon from 2-benzotriazolylethylsilanes provides a versatile method for the introduction of 1-arylethenyl moieties into organic molecules. The 2-benzotriazolylethyl moieties act as masked 1-arylethenyl units that can be transformed into the corresponding alkene when needed. The vicinal elimination of silicon can be accomplished by several protocols, including pyrolysis, [1,4]-Brook rearrangement, and fluoride ion induced β-elimination. Examples are documented illustrating potentially general methods for the preparation of styrenes, 1,2-disubstituted allyl alcohols, α-substituted acrylamides, 1,3-disubstituted homoallyl alcohols, and γ,δ-unsaturated ketones. A new example of a Grovenstein-Zimmerman rearrangement is observed as a secondary process during the synthesis of enones.

A general regiospecific method for the synthesis of *p*-nitroaryl-diarylmethanes has been developed starting from diarylmethanols and 2- and/or 3- substituted nitrobenzenes. This utilizes the quantitative condensation between benzotriazole and diarylmethanols under acidic catalysis and in the presence of perfluorocarbon fluids, followed by vicarious nucleophilic substitution of the resulting diarylmethylbenzotriazoles upon nitrobenzenes in moderate to high yield. These vicarious nucleophilic substitutions complement Friedel-Crafts reactions for the synthesis of triarylmethanes. Oxidative nucleophilic substitution of hydrogen, which is observed as a side process during vicarious nucleophilic substitution, is utilized for the synthesis of 4-nitrobenzophenones.

CHAPTER 1
GENERAL INTRODUCTION

The importance of carbon–carbon bond formation in organic chemistry can not be overemphasized. While functional group transformations give an organic molecule its cast, carbon–carbon bond forming provides the backbone. By utilizing these two major "battle fields", organic chemists can meet the growing need for molecules that are able to fit into a given molecular environment and bind efficiently to specific receptors (for recent reviews on molecular recognition see [96AG(E)2589, 97CBR23]).

Benzotriazole is an effective synthetic auxiliary. It is cheap and readily recycled while most of its derivatives are stable and easy to prepare. The two characteristics of benzotriazole that make it an excellent carbon–carbon bond forming agent are its leaving group ability and its behavior as activator towards proton loss [95S1315]. This work shows how these two features can be interwoven to accomplish the ultimate goal of carbon–carbon bond formation.



1.1 **1.2** **1.3**

Figure 1.1

The general approach described in this work is best shown in Figure 1.1. The hydrogen atom in **1.1** can be easily abstracted to afford **1.2** because of the aromaticity of the benzotriazole ring, and the existence of electron-attracting pyridine-like nitrogen atoms [95S1315]. This process is regiospecific and occurs only when either X or R or both are activating groups. Throughout this work the α-position in **1.1** is activated by one aryl

group (Chapter 2, 4 and 5), by two aryl groups (Chapter 5) or by the trimethylsilyl group (Chapter 3).

The carbanion **1.2** can be trapped by electrophiles (E) to afford the "α-benzotriazolylalkylation" product **1.3**. Aldehydes, ketones, acid chlorides, isocyanates, enones, oxiranes, alkyl halides and electron-deficient arenes all react cleanly and efficiently with **1.2** at temperatures ranging from –78 °C (Chapters 2, 3, and 4) to –20 °C (Chapter 5) to afford adducts **1.3** thus proving the generality of this reaction. The nature of these reactions allow for "one-pot" procedures, wherein the adduct **1.3** can be further transformed into products without isolation (Chapter 2).

The elimination of benzotriazole from **1.3** is the key step of this methodology. New, milder and more efficient methods for benzotriazole elimination comprise the scope of this work. One of the most frequently used reagent for benzotriazole elimination is $ZnBr_2$. When E is an aldehyde or a ketone (Figure 1.1), the resulting alkoxide underwent a pinacol-type rearrangement during which departure of the complexed benzotriazole was assisted by the migration of an adjacent carbon atom to afford the carbon-insertion product (Chapter 2). When R = $SiMe_3$ while X = OMe, the reaction of **1.2** with aldehydes or ketones underwent the expected Peterson olefination to afford the enol ethers which were hydrolyzed with $ZnBr_2$ and acid to the corresponding one-carbon homologated carboxylic acids (Chapter 3). A new method of benzotriazole removal was revealed when **1.2** was reacted with nitro-arenes in presence of excess base. The σ^H adducts that are formed as intermediates underwent base promoted elimination of benzotriazole to give C-linked functionalized nitroarenes (Chapter 5). The substrates **1.1** where X = CH_2SiMe_3 and R = aryl react following the approach shown in Figure 1.1, while the elimination of benzotriazole is accomplished by vicinal elimination of silicon by one of three processes depending upon the structure of the electrophile: pyrolysis, [1,4] C→O Brook rearrangement, or fluoride induced β-elimination to afford the corresponding terminal alkenes.

In summary, a study of a variety of C–C bond forming reactions has been undertaken with benzotriazole as a synthetic auxiliary. These reactions include regiospecific insertion of an aryl- and heteroaryl-bearing carbon, homologation of aldehydes and ketones to the corresponding carboxylic acids, nucleophilic substitution of hydrogen in nitroarenes with carbon nucleophiles, and α-aryl-alkenylation of a variety of aldehydes, oxiranes, alkyl halides, isocyanates and acyl chlorides.

CHAPTER 2
GENERAL AND EFFICIENT INSERTIONS OF CARBONS CARRYING ARYL AND HETEROARYL GROUPS: SYNTHESIS OF ALPHA-ARYL- AND ALPHA-HETEROARYL-SUBSTITUTED KETONES

2.1 Introduction

Carbon chain extension or ring expansion of carbonyl compounds by a one carbon unit is a frequently encountered synthetic objective and has attracted widespread and continuing interest (for recent examples, see [95T703, 92TL7543, 92TL7181, 90BCJ1266, 94JOC4725, 94S1283, 94JCS(CC)2289, 87JA4124, 87T3]). Carbon insertion is the most straightforward and most commonly used strategy for this purpose. The numerous procedures for the insertions of carbons bearing C-linked substituents into aldehydes and ketones available in the literature can be classified into the following categories: (i) diazo insertion reactions utilizing ethyl diazoacetate [89JOC3258, 83S197, 77JOC459], α-diazo ketones and aldehydes [90JOC5297], diazoalkanes [94JOC4725, 94S1283] and aryldiazomethanes [83JOC4407, 55JA109]; (ii) β-oxido carbenoid chemistry as initiated by Yamamoto using dihalomethyllithiums [74JA6510, 76TL2617], and recently extensively developed by Yamakawa [95T703, 92TL7543, 92TL7181, 90BCJ1266] with chloromethyl sulfoxides as advantageous reagents for the insertions of carbons bearing an alkyl [92TL7181, 79S968] or an aryl [79S968] group into aldehydes and ketones; (iii) semipinacol-type rearrangements: alkylidene insertions utilizing α-lithioalkyl sulfoxides [87JOC774] and selenoxides [87JOC774, 83JOC2098, 82TL983, 88TL3265, 84TL2713] and arylmethylene insertions *via* the rearrangement of halohydrins, derived from the addition of benzylmagnesium chloride to carbonyl compounds,

followed by α-bromination [67TL5327, 70JOC2670, 71JOC2030]; (iv) other approaches include ring expansions of cyclic ketones *via* radical processes [91TL6575, 87JA3493, 90JOC5442] and more complex pathways [95JOC2748].

While several arylmethylene insertion routes to one carbon homologated α-aryl substituted ketones are available as mentioned above, insertions of carbons carrying heteroaryl groups into carbonyl compounds were previously unknown. Moreover, all the previous approaches possess limitations: (i) Direct insertions of the corresponding aryl diazomethanes [83JOC4407, 55JA109] are not suitable for large scale preparations and often suffer from epoxide formation and multiple homologation; (ii) The original β-oxido carbenoid route is limited by the extreme thermal instability of the (α,α-dibromobenzyl)lithium reagent [82TL983]; (iii) Sisti's semipinacol type rearrangement [67TL5327, 70JOC2670, 71JOC2030] involves three steps and is limited to cyclic ketones.

A systematic investigation of the benzotriazole-mediated insertion route to one carbon chain extended or ring expanded α-functionalized ketones has been undertaken. Full detail for the insertions of carbons carrying aryl and heteroaryl groups to furnish one carbon homologated α-aryl and α-heteroaryl substituted ketones is given and comments on the generality of and significant exceptions to the scope of this synthetic transformation are presented. Substituent effects on relative migration rates are also described.

2.2 Results and Discussion

Preparation of 1-(arylmethyl)- and 1-(heteroarylmethyl)-benzotriazoles **2.1a-f** and *in situ* preparation of their lithio derivatives **2.4a-f.** 1-(4-Methylbenzyl)benzotriazole (**2.1a**)(see Chapter 4 compound **4.1b**), 1-(4-*N*,*N*-dimethylaminobenzyl)benzotriazole (**2.1b**) [90S341], 1-(1-methylindol-3-ylmethyl)benzotriazole (**2.1d**) [95SC539] and 1-(4-methoxybenzyl)benzotriazole (**2.1e**) [91CB1819] were synthesized according to previously reported procedures. 1-(5-Methylthien-2-ylmethyl)benzotriazole (**2.1c**) was

produced by the treatment of 1-hydroxymethylbenzotriazole with 2-methylthiophene in refluxing acetic acid in 50% yield. 1-(4-Chlorobenzyl)benzotriazole (**2.1f**) was prepared in good yield from the reaction of 4-chlorobenzyl chloride with benzotriazole in refluxing toluene. All of these benzotriazole derivatives **2.1a-f** can easily be prepared on a large scale; novel compound **2.1c** was characterized by NMR spectroscopy and elemental analyses.

Lithio derivatives **2.4a-f** were prepared *in situ* as deep green solutions in THF under argon by stirring compounds **2.1** with *n*-butyllithium at –78 °C for *ca* 30 min (Scheme 2.1). Anions **2.4d** and **2.4e** have been previously documented to react readily with electrophiles followed by the displacement of the benzotriazolyl group to furnish functionalized indoles [95SC539], carbazoles [95JOC3707] and methoxybenzenes [91CB1819].

Arylmethylene and heteroarylmethylene insertions into aldehydes and ketones: preparation of α-aryl and α-heteroaryl substituted ketones. Treatment of the deep green solutions of **2.4** prepared *in situ* with aldehydes or ketones at –78 °C for 4 h gave the intermediate products **2.5** (Figure 2.1). The intermediates **2.5** thus produced were shown in each case to be capable of *in situ* rearrangement promoted by an approximately three fold molar excess of zinc bromide upon heating to furnish one carbon homologated α-aryl and α-heteroaryl substituted ketones **2.2a-t** in moderate to excellent yields (Tables 2.1 and 2.2). All compounds prepared showed the expected NMR spectra and all new compounds were further characterized by elemental analyses (see experimental section).

Zinc bromide is necessary for the departure of the benzotriazolyl group. An excess of the Lewis acid and complete coordination of the oxygen anion with zinc cation were found to be crucial to suppress the tendency of intermediates **2.5** to revert back to the starting materials. The reaction temperatures necessary for the rearrangement vary as listed in Tables 2.1 and 2.2. As expected the greater the degree of R group stabilization (Figure 2.1) of the transient cation **2.7**, the lower the temperature needed to complete the

rearrangement. In those cases where the required temperature was higher than the boiling point of THF, the THF was distilled off and an appropriate solvent (or no solvent) was added for the rearrangement stage.

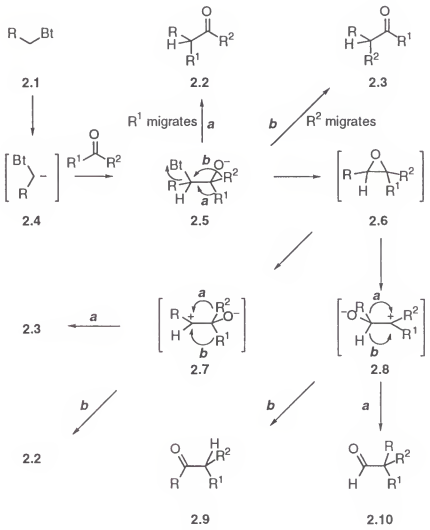


Figure 2.1

Of special importance is the general applicability of these insertions to a diverse aldehydes and ketones. While Table 2.1 shows examples of insertions into aliphatic and aromatic aldehydes and acyclic ketones to give chain extended products, Table 2.2 illustrates the successful insertions into cyclic ketones to provide ring expanded ketones.

Table 2.1. Arylmethylene and Heteroarylmethylene Insertions into Aldehydes and Acyclic Ketones: Preparation of One-Carbon Chain-Extended Ketones

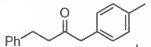
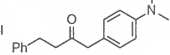
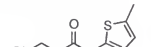
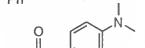
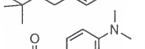
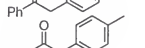
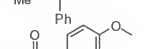
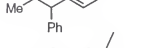
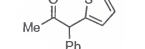
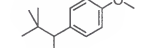
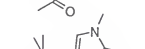
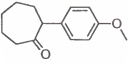
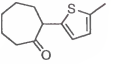
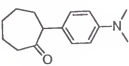
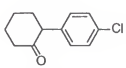
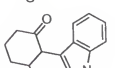
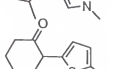
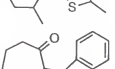
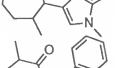
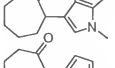
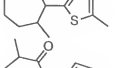
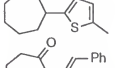
entry	carbonyl compound	Bt-reagent	temp / °C / time, h /solvent	product	yield (%)
1		**2.1a**	150/10/neat		**2.2a** 65
2		**2.1b**	115/5/ $CHCl_2CH_2Cl$		**2.2b** 63
3		**2.1c**	115/8/ $CHCl_2CH_2Cl$		**2.2c** 76
4		**2.1b**	140/0,5/ neat		**2.2d** 76
5		**2.1b**	65/10/THF		**2.2e** 40
6		**2.1a**	210/3/neat		**2.2f** 32
7		**2.1e**	180/3/neat		**2.2g** 79
8		**2.1c**	115/8/ $CHCl_2CH_2Cl$		**2.2h** 90
9		**2.1e**	175/3/neat		**2.2i** 63
10		**2.1d**	65/3/THF		**2.2j** 87
11		**2.1e**	155/3/neat		**2.2k** 35

Table 2.2. Arylmethylene and Heteroarylmethylene Insertions into Cyclic Ketones: Preparation of One-Carbon Ring-Expanded Ketones

entry	carbonyl compound	Bt-reagent	temp / °C / time, h /solvent	product		yield (%)
1		**2.1e**	115/5/ $CHCl_2CH_2Cl$		**2.2l**	40
2		**2.1c**	115/5/ $CHCl_2CH_2Cl$		**2.2m**	66
3		**2.1b**	140/1/ neat		**2.2n**	40
4		**2.1f**	170/12/neat		**2.2o**	85
5		**2.1d**	65/10/ THF		**2.2p**	85
6		**2.1c**	115/10/ $CHCl_2CH_2Cl$		**2.2q**	67
7		**2.1d**	65/10/ THF		**2.2r**	81
					**2.3r**	3
8		**2.1c**	115/10/ $CHCl_2CH_2Cl$		**2.2s**	66
					**2.3s**	16
9		**2.1g**	110/10/ toluene		**2.2t**	60

The regioselectivity of these insertions is also significant. In most cases (entries 1-10 in Table 1 and entries 1-6 in Table 2.2), single regioisomers were produced by migration of the group (R^1, see Scheme 2.1) which can best stabilize an electron deficiency in the transition state, *i.e.* in general H > Ar > alkyl; *t*-alkyl > *s*-alkyl > *n*-alkyl. Similar migration aptitudes were found in other pinacol-type rearrangements [91COS(3)705]. Although the yields of **2.2e** and **2.2f** were only moderate, no other regioisomers were detected according to GCMS analysis of the crude products; the relatively low yields of **2.2e** and **2.2f** were due either to the partial recovery of the intermediates **2.5** or to the reverse reaction of **2.5** to the starting materials. In the case of **2.2k** (entry 11 in Table 2.1), the alternative regioisomer **2.3k**, derived from the migration of the trifluorophenyl group (R^2, see Scheme 2.1), was formed in 27% yield based on the GCMS and NMR results of the crude product, although its separation was not achieved.

Two different insertion reagents each reacted with 2-methylcyclohexanone (entries 7 and 8 in Table 2.2), to afford two regioisomers (**2.2** and **2.3**) in each case. In the case of entry 7, **2.2r** and **2.3r** were separated in yields of 81% and 3%, and the GCMS analysis of the crude reaction mixture indicated that they were formed in a ratio of 11:1. In the case of entry 8, **2.2s** and **2.3s** were formed in a ratio of 5:1 according to the GCMS of the crude product, although only **2.2s** was separated in 66% yield. These results again reveal preferential migrations of the most substituted alkyl group.

Within this group it was demonstrated that the alkoxymethylene and thioalkoxymethylene insertions proceeded through the epoxide intermediates by successful isolation of the latter [96JOC7564]. Epoxide intermediates seem unlikely in most of the present reactions, since in not one of the cases described in Tables 2.1 and 2.2 were any of the regioisomers **2.9** and **2.10** (Figure 2.1) detected. If epoxides **2.6** were intermediates, formation of compounds **2.9** and **2.10** would be expected alongside insertion products **2.2** and **2.3**, especially in the cases of entries 6-8 and 11 of Table 2.1 where the corresponding tertiary cationic species **2.8** (Figure 2.1) should be more stable than

secondary cationic species **2.7**. However, the epoxide mechanism was implicated in one experiment as shown in Figure 2.2. Treatment of the anion of 1-(4-methoxybenzyl)benzotriazole (**2.1e**) with *p*-tolualdehyde, followed by zinc bromide assisted rearrangement, gave an inseparable mixture of ketones **2.2u** and **2.9u** together with aldehyde **2.10u** in the ratio of 3:1:12 in total 88% yield based on the NMR and GCMS results of the crude product. These results suggest that epoxide **2.6** is the intermediate (Figure 2.1), which can open up from both sides to give cationic intermediates **2.7** and **2.8**. While **2.7** leads to the "normal" insertion

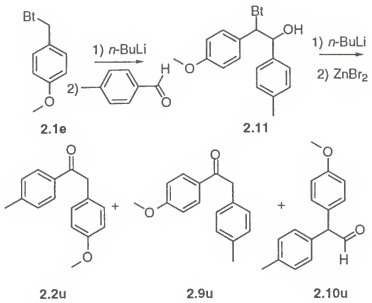


Figure 2.2

product **2.2u** (*via* path ***a***, hydride migration), subsequent hydride (path ***a***) and 4-methoxyphenyl (path ***b***) migrations of **2.8** furnish ketone **2.9u** and aldehyde **2.10u**. It is noteworthy that in this case the 4-methoxyphenyl group migrates preferentially over the hydrogen due to the existence of the electron donating methoxy group which reflects a significant substituent effect on the migration aptitude. The reason for the different behavior in the case of **2.1e** from all those in Tables 2.1 and 2.2 has not been fully clarified. However, the diastereoselectivity of the initial addition does not determine product structures since for the reaction described in Figure 2.2 the same products were obtained in

the same proportions when the two diastereoisomers of adduct intermediate **2.11** were isolated and treated separately with $ZnBr_2$.

An important limitation of this methodology is that the rearrangement fails with substrates **2.1** where R is a group that does not favor the formation of the carbocation **2.7** (Figure 2.1). Even though the addition of carbanions **2.4** to carbonyl to give **2.5** when R = H, 4-fluorophenyl or carboxylate were high yielding reactions, none of them underwent rearrangement to the corresponding insertion products.

To explore further the generality of this insertion methodology, 1-(3-phenylallyl)benzotriazole (**2.1g**) was prepared from the reaction of cinnamyl bromide with benzotriazole in the presence of sodium ethoxide in ethanol in 52% yield. The scope of this methodology was thus extended to vinyl-substituted methylene insertions as exemplified by the successful preparation of 2-(2-phenylvinyl)cycloheptanone (**2.2t**) from 1-(3-phenylallyl)benzotriazole (**2.1g**) and cyclohexanone (Table 2.2, entry 9). However, a stabilizing group such as phenyl at the vinylic terminal to assist the departure of the benzotriazolyl group in **2.5** (Figure 2.1) was found to be essential since the simple allyl analog 1-allylbenzotriazole failed to give homologation products: even at 220 °C for 10 h, the intermediate **2.5** was still present, while higher temperatures caused tar formation. Vinyl-substituted methylene homologations of ketones have previously been accomplished by direct insertion of the corresponding diazo compounds [94JOC4725, 94S1283] and a rather complex radical process [91TL6575].

Substituent effects on relative migration rates. To gain insight into the mechanism of this reaction, we examined the electronic effects of the substituents on the transition state. 1-(4-Methoxybenzyl)benzotriazole (**2.1e**) was used for insertion into a series of *p*-substituted benzophenones according to our methodology (Figure 2.3). The reaction conditions were those used for the synthesis of **2.2k** (Table 2.1, entry 11) *i.e.* heating at 155 °C for 3 hours without solvent. Under these conditions, solvent and steric influences upon variation in the migration rates are minimized. The crude mixture of products was

analyzed by GCMS, and the identities of the two products **2.2** and **2.3** were assigned according to their fragmentation patterns: a peak at m/z 105 was diagnostic for the product containing unsubstituted benzoyl group. The migration ratio of substituted phenyl to give product **2.2** and of unsubstituted phenyl to form product **2.3** was calculated. This ratio represents the relative migration aptitude of a substituted phenyl free of steric and solvent

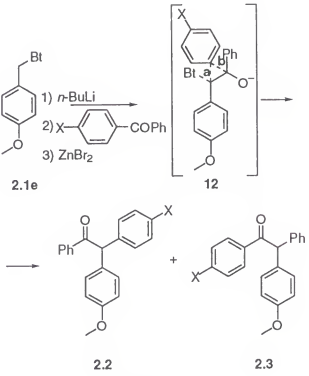


Figure 2.3

effects. The data are presented in Table 2.3. When $\log(k_X/k_H)$ was plotted against the corresponding σ and σ^+ values [91CR165] (Figure 2.4), the corresponding ρ and ρ^+ values were obtained (Table 2.3). The linear correlation is better for ρ^+ (correlation coefficient 0.982) than for ρ (correlation coefficient 0.946) (Figure 2.4). The negative value for the selectivity parameter (ρ^+) signifies that electron-donating substituents accelerate the migration rate and suggests that bond making (of bond **a**) is further advanced in the transition state **2.12** than bond breaking (of bond **b**)(see Figure 2.3). A correlation with σ^+ rather than with σ was found, indicating that conjugative electronic interaction in

Table 2.3 Hammett Correlations

X	*p*-OCH_3	*p*-CH_3	*p*-F	*p*-H	*p*-Cl	*p*-Br	*p*-CF_3
k_X/k_H	5.75	2.45	1.24	1	0.74	0.59	0.37
$\log(k_X/k_H)$	0.760	0.389	0.093	0	–0.131	–0.229	–0.432
σ	–0.27	–0.17	0.06	0	0.23	0.23	0.54
σ^+	–0.78	–0.31	–0.07	0	0.11	0.15	0.61
$\rho(r)$			$-1.39^c(0.946)^b$				
$\rho^+(r)$			$-0.92^a(0.982)^b$				

[a] $\log(k_X/k_H)$ plotted against σ^+ for ρ^+. [b] Correlation coefficient. [c] $\log(k_X/k_H)$ plotted against σ for ρ

the transition state between ring substituent and the cationic center dominates over field effects.The small $|\rho^+|$ value indicates (i) an early, reagent-like transition state [84JA3230], similar to a phenonium ion where β-aryl group assists leaving of the benzotriazole [72MI1] and (ii) a small contribution from cationic structures of types **2.8** to the transition state (Figure 2.1) since if **2.8** was important, the $|\rho^+|$ value should have been much higher (higher than 3) due to strong interaction between the C_α carbocation and the substituent.

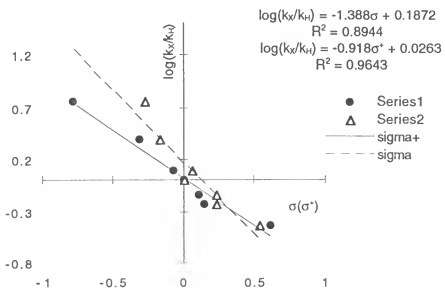


Figure 2.4 Hammett Plot

Thus, the Hammett correlation implicates an early reagent-like transition state with cationic character for this process.

2.3 Conclusion

Various 1-arylmethyl- and 1-heteroarylmethyl-benzotriazoles are excellent insertion reagents for the transformations of aldehydes and ketones into one-carbon chain-extended or ring-expanded α-aryl and α-heteroaryl substituted ketones. Advantages of this methodology include wide generality, excellent regioselectivity in many cases, ready availability of starting materials and simple one-pot procedures.

2.4 Experimental Section

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. 1-(4-Methylbenzyl)benzotriazole (**2.1a**), 1-(4-*N*,*N*-dimethylaminobenzyl)-benzotriazole (**2.1b**) [90S341], 1-(1-methylindol-3-ylmethyl)benzotriazole (**2.1d**) [95SC539] and 1-(4-methoxybenzyl)benzotriazole (**2.1e**) [91CB1819] were prepared according to previously reported procedures.

2.4.1 Preparation of 5-Methyl-2-(benzotriazol-1-ylmethyl)thiophene (**2.1c**).

A mixture of 1-hydroxymethylbenzotriazole (4.5 g, 30 mmol) and 2-methylthiophene (3.4 g, 35 mmol) in glacial acetic acid (50 mL) was refluxed for 48 h. After the acetic acid was distilled off under reduced pressure, aqueous sodium hydroxide

(5%, 30 mL) and chloroform (50 mL) were added. The organic layer was separated, washed with water (50 mL) and dried ($MgSO_4$). After the solvent was removed, the residue was crystallized from methylene chloride and hexanes to give the pure product as a brownish solid (3.4 g, 50%), mp 108-109 °C: ^{1}H NMR δ 2.40 (s, 3 H), 5.92 (s, 2 H), 6.60 (d, J = 3.4 Hz, 1 H), 6.90 (d, J = 3.4 Hz, 1 H), 7.35 (dd, $J_1 = J_2$ = 6.7 Hz, 1 H), 7.46 (m, 2 H), 8.05 (d, J = 8.3 Hz, 1 H); ^{13}C NMR δ 15.4, 47.2, 109.6, 120.0, 123.8, 125.0, 127.3, 127.4, 132.3, 134.0, 141.3, 146.2; Anal. Calcd for $C_{12}H_{11}N_3S$: C, 62.86; H, 4.84; N, 18.33. Found: C, 62.52; H, 4.79; N, 18.33.

2.4.2 Preparation of 1-(4-Chlorobenzyl)benzotriazole (**2.1f**).

A solution of benzotriazole (23.8 g, 200 mmol) and 4-chlorobenzyl chloride (22.5 g, 140 mmol) in toluene (200 mL) was refluxed for 48 h. After cooling to room temperature, the solution was washed with aqueous sodium hydroxide (5%, 2 × 100 mL) and water (100 mL) to remove excess benzotriazole. The toluene solution was then extracted with cold hydrochloric acid (25%, 5 × 50 mL) to allow complete extraction of the product into the aqueous layer. To the combined aqueous extract was added water (500 mL) and the solution extracted with benzene (3 × 100 mL). The combined benzene solution was washed with water (2 × 50 mL) and dried ($MgSO_4$). After the solvent was removed, the residue was crystallized from methanol to give a white solid (22.5 g, 66%), mp 101-102 °C (lit. [79AP806] mp 90 °C): ^{1}H NMR d 5.78 (s, 2 H), 7.18 (d, J = 8.3 Hz, 2 H), 7.27 (d, J = 8.3 Hz, 2 H), 7.33-7.42 (m, 3 H), 8.04 (d, J = 8.0 Hz, 1 H); ^{13}C NMR d 51.2, 109.4, 119.8, 123.9, 127.4, 128.8, 129.0, 132.5, 133.1, 134.2, 146.1; Anal. Calcd for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.02; H, 3.88; N, 17.36.

2.4.3. Preparation of (*E*)-3-(Benzotriazol-1-yl)-1-phenyl-1-propene (**2.1g**).

To a solution of sodium ethoxide prepared from sodium metal (2.3 g, 100 mmol) in ethanol (200 mL) were added benzotriazole (13.1 g, 110 mmol) and cinnamyl bromide (19.7 g, 100 mmol). The mixture was refluxed overnight. After the ethanol was removed, benzene (200 mL) was added and the solution was washed with aqueous sodium hydroxide (5%, 2 × 100 mL) and water (100 mL) to remove excess benzotriazole. The benzene solution was then extracted with cold hydrochloric acid (25%, 3 × 100 mL) to allow complete extraction of the product into the aqueous solution. To the combined aqueous extract was added water (500 mL) and the solution extracted with benzene (3 × 100 mL). The combined benzene solution was washed with water (2 × 50 mL) and dried ($MgSO_4$). Removal of the solvent gave white prisms (12.2 g, 52%), mp 79 °C (lit. [95JHC1325] mp 75–76 °C): ^{1}H NMR δ 5.37 (dd, *J* = 6.2 and 1.4 Hz, 2 H), 6.34 (dt, *J* = 15.8 and 6.2 Hz, 1 H), 6.62 (dt, *J* = 15.8 and 1.4 Hz, 1 H), 7.21–7.35 (m, 6 H), 7.41 (td, *J* = 8.3 and 1.0 Hz, 1 H), 7.52 (dd, *J* = 8.3 and 1.0 Hz, 1 H), 8.05 (dd, *J* = 8.3 and 1.0 Hz, 1 H); ^{13}C NMR δ 50.3, 109.6, 119.8, 122.0, 123.7, 126.4, 127.1, 128.1, 128.5, 132.7, 134.2, 135.4, 146.1; Anal. Calcd for $C_{15}H_{13}N_3$: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.52; H, 5.55; N, 17.90.

2.4.4. General Procedure for the Insertions into Aldehydes and Ketones: Preparation of -Aryl and -Heteroaryl Substituted Ketones **2.2a–s**, **2.3r–s** and 2-((*E*)-2-Phenylethenyl)cycloheptanone (**2.2t**).

To a solution of an appropriate benzotriazole derivative (5 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (2 *M*, 2.8 mL, 5.5 mmol). After 30 min, a solution of an appropriate aldehyde or ketone (5.5 mmol) in THF (10 mL) was added. The mixture was stirred at –78 °C for an additional 4 h and allowed to warm to room temperature overnight. A solution of zinc bromide (15 mmol) in THF (15 mL) was then added. As indicated in Table 2.1, (i) the mixture was refluxed in THF (for entries 5 and 10 in Table 2.1, and entries 5 and 7 in Table 2.2), or (ii) the THF was removed, an

appropriate solvent (15 mL) added and the mixture refluxed (for entries 2, 3 and 8 in Table 2.1, and entries 1, 2, 6, 8 and 9 in Table 2.2), or (iii) the THF was removed and the residue was heated at an appropriate temperature (for entries 1, 4, 7, 9, and 11 in Table 2.1, and 3 and 4 in Table 2.2). Ethyl acetate (150 mL) and diethyl ether (100 mL) were added to the residue and the mixture was stirred for 1 h at room temperature. The solid was filtered off and the solution was washed with water (2 × 100 mL) and dried ($MgSO_4$). After the solvent was removed, the residue was subjected to column chromatography to give the pure product.

1-(4-Methylphenyl)-4-phenyl-2-butanone (**2.2a**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid, mp 65–66 °C: ^{1}H NMR δ 2.31 (s, 3 H), 2.70–2.76 (m, 2 H), 2.81–2.87 (m, 2 H), 3.59 (s, 2 H), 7.01–7.26 (m, 9 H); ^{13}C NMR δ 21.0, 29.7, 43.3, 49.9, 126.0, 128.2, 128.4, 129.2, 129.4, 131.0, 136.5, 140.9, 207.5; Anal. Calcd for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 86.00; H, 7.74.

1-(4-*N*,*N*-Dimethylaminophenyl)-4-phenyl-2-butanone (**2.2b**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid, mp 42–43 °C: ^{1}H NMR δ 2.71 (t, *J* = 8.0 Hz, 2H), 2.83 (t, *J* = 8.0 Hz, 2H), 2.89 (s, 6H), 3.52 (s, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 7.01 (d, *J* = 8.6 Hz, 2H), 7.08–7.24 (m, 5H); ^{13}C NMR δ 29.7, 40.4, 42.9, 49.4, 112.8, 121.7, 125.8, 128.2, 128.3, 129.8, 141.0, 149.5, 208.2; Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 81.11; H, 8.09; N, 4.94.

1-(5-Methylthien-2-yl)-4-phenyl-2-butanone (**2.2c**).

Hexanes:diethyl ether (2:1) was used as the eluent to give a white solid, mp 43–44 °C: ^{1}H NMR δ 2.42 (s, 3H), 2.65–2.92 (m, 4H), 3.73 (s, 2H), 6.57–6.59 (m, 2H), 7.12–7.25 (m, 5H); ^{13}C NMR δ 15.2, 29.7, 43.0, 44.0, 125.0, 126.0, 126.6, 128.2, 128.4, 132.7, 139.5, 140.8, 206.0; Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60. Found: C, 73.88; H, 6.64.

1-(4-*N*,*N*-Dimethylaminophenyl)-3,3-dimethyl-2-butanone (**2.2d**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid, mp 34-36 °C: ^{1}H NMR δ 1.17 (s, 9H), 2.89 (s, 6H), 3.68 (s, 2H), 6.68 (d, *J* = 8.8 Hz, 2H), 7.04 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 26.4, 40.6, 42.3, 44.4, 112.7, 122.7, 130.0, 149.4, 213.4; Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.26; H, 9.72; N, 6.36.

1-Phenyl-2-(4-*N*,*N*-dimethylaminophenyl)ethanone (**2.2e**).

Hexanes:diethyl ether (1:1) was used as the eluent to give a white solid, mp 119–120 °C (lit. [30JA4495] mp 128 °C): ^{1}H NMR δ 2.88 (s, 6H), 4.15 (s, 2H), 6.67 (d, *J* = 7.0 Hz, 2H), 7.12 (d, *J* = 7.0 Hz, 2H), 7.37–7.52 (m, 3H), 7.99 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR δ 40.5, 44.5, 112.8, 122.1, 128.4, 128.5, 129.9, 132.8, 136.6, 149.5, 198.1; Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.59; H, 7.19; N, 5.75.

1-(4-Methylphenyl)-1-phenyl-2-propanone (**2.2f**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil (lit. [58JOC971] bp 143–148 °C /0.25mm): ^{1}H NMR δ 2.19 (s, 3H), 2.29 (s, 3H), 5.06 (s, 1H), 7.11 (m, 4H), 7.19-7.31 (m, 5H); ^{13}C δ NMR 20.9, 29.8, 64.5, 127.0, 128.5, 128.7, 128.8, 129.3, 135.2, 136.8, 138.4, 206.5; HRMS Calcd for $C_{16}H_{16}O$: 224.1201, Found: 224.1211.

1-(4-Methoxyphenyl)-1-phenyl-2-propanone (**2.2g**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil (lit. [28BSF868] bp 225 °C /25mm): ^{1}H NMR δ 2.20 (s, 3H), 3.75 (s, 3H), 5.05 (s, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 7.19-7.31 (m, 5H); ^{13}C NMR δ 29.8, 55.1, 64.1, 114.0, 127.0, 128.6, 128.8, 129.9, 130.3, 138.6, 158.7, 206.6; HRMS Calcd for $C_{16}H_{16}O_2$: 241.1229 (M+1), Found: 241.1227.

1-(5-Methylthien-2-yl)-1-phenyl-2-propanone (**2,2h**).

Hexanes:diethyl ether (2:1) was used as the eluent to give a colorless oil: ^{1}H NMR δ 2.19 (s, 3H), 2.39 (s, 3H), 5.17 (s, 1H), 6.56–6.57 (m, 1H), 6.61–6.63 (m, 1H), 7.26–7.31 (m, 5H); ^{13}C NMR δ 15.1, 29.0, 59.9, 124.5, 126.0, 127.4, 128.4, 128.7, 138.1, 138.2, 139.6, 204.7; Anal. Calcd for $C_{14}H_{14}OS$: C, 73.01; H, 6.13. Found: C, 72.83; H, 6.17.

4,4-Dimethyl-3-(4-methoxyphenyl)- 2-pentanone (**2,2i**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil: ^{1}H NMR δ 0.97 (s, 9H), 2.06 (s, 3H), 3.54 (s, 1H), 3.79 (s, 3H), 6.84 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H); ^{13}C NMR δ 27.8, 32.3, 34.3, 55.1, 67.1, 113.4, 127.9, 131.3, 158.7, 209.1; HRMS Calcd for $C_{14}H_{21}O_2$: 221.1542 (M+1), Found: 221.1541.

4,4-Dimethyl-3-(1-methylindol-3-yl)-2-pentanone (**2,2j**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a white solid, mp 65 °C: ^{1}H NMR δ 1.04 (s, 9 H), 2.10 (s, 3 H), 3.73 (s, 3 H), 3.96 (s, 1 H), 6.99 (s, 1 H), 7.12 (dd, J_1= J_2 = 8.0 Hz, 1 H), 7.21 (dd, J_1 = J_2 = 8.0 Hz, 1 H), 7.28 (d, J = 8.0 Hz, 1 H), 7.65 (d, J = 8.0 Hz, 1 H); ^{13}C NMR δ 28.1, 32.5, 32.7, 34.9, 58.1, 109.0, 109.2, 119.0, 119.1, 121.4, 128.8, 129.0, 136.6, 209.7; Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.96; H, 8.91; N, 5.53.

1-(4-Trifluoromethylphenyl)-2-(4-methoxyphenyl)-2-phenylethanone (**2,2k**).

Hexanes:diethyl ether (4:1) was used as the eluent to give colorless prisms, mp 84–85 °C: ^{1}H NMR δ 3.75 (s, 3H), 5.95 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 2H), 7.22–7.35 (m, 5H), 7.64 (d, J = 8.0 Hz, 2H), 8.07 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 55.2, 59.1, 114.3, 123.5 (q, J = 271.0 Hz), 125.6 (q, J = 4.8 Hz), 127.3, 128.8, 129.0, 129.2, 130.1, 130.4, 134.1(q, J = 32.6 Hz), 138.8, 139.5, 158.9, 197.5; Anal. Calcd for $C_{22}H_{17}OF_3$: C, 71.35; H, 4.63. Found: C, 71.22; H, 4.47.

2-(4-Methoxyphenyl)cycloheptanone (**2.21**).

Hexanes:diethyl ether (3:1) was used as the eluent to give colorless plates, mp 59–60 °C (from petroleum ether) (lit. [58JOC1] mp 59–60 °C): ^{1}H NMR δ 1.39–1.64 (m, 3H), 1.89–2.15 (m, 5H), 2.44–2.52 (m, 1H), 2.61–2.71 (m, 1H), 3.65 (dd, *J* =11.3 and 4.1 Hz, 1H), 3.77 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 25.3, 28.4, 29.9, 31.9, 42.3, 55.1, 57.8, 113.8, 128.7, 132.3, 158.4, 213.6.

2-(5-Methylthien-2-yl)cycloheptanone (**2.2m**).

Hexanes:diethyl ether (3:1) was used as the eluent to give a colorless oil: ^{1}H NMR δ 1.27–1.62 (m, 3H), 1.78–2.10 (m, 4H), 2.15–2.30 (m, 1 H), 2.41 (s, 3H), 2.42–2.50 (m, 1H), 2.65–2.73 (m, 1H), 3.85 (dd, *J* = 11.1 and 4.7 Hz, 1H), 6.58 (d, *J* = 3.5 Hz, 1 H), 6.65 (d, *J* = 3.5 Hz, 1H); ^{13}C NMR δ 15.1, 25.5, 27.8, 29.8, 32.6, 41.2, 54.2, 124.1, 124.6, 138.6, 139.8, 211.6; Anal. Calcd for $C_{12}H_{16}OS$: C, 69.19; H, 7.74. Found: C, 69.33; H, 7.88.

2-(4-*N*,*N*-Dimethylaminophenyl)cycloheptanone (**2.2n**).

Hexanes:diethyl ether (1:1) was used as the eluent to give a yellowish solid, mp 70–72 °C: ^{1}H NMR δ 1.36–1.60 (m, 3H), 1.85–2.15 (m, 5H), 2.39–2.46 (m, 1H), 2.63–2.72 (m, 1H), 2.90 (s, 6H), 3.59 (dd, *J* =11.3 and 4.2 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 25.6, 28.1, 30.1, 31.5, 40.5, 42.0, 57.9, 112.7, 127.8, 128.2, 149.5, 213.8; Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.63; H, 9.32; N, 5.80.

2-(4-Chlorophenyl)cyclohexanone (**2.2o**).

Hexanes:diethyl ether (3:1) was used as the eluent to give white plates, mp 81-82 °C (lit. [58JOC1] mp 77–78 °C): ^{1}H NMR δ 1.77–2.50 (m, 8H), 3.57 (dd, *J* = 11.9 and 5.4 Hz, 1H), 7.05 (d, *J* = 8.5 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 25.3, 27.7, 35.2, 42.1, 56.7, 128.4, 129.9, 132.6, 137.2, 209.6; Anal. Calcd for $C_{12}H_{13}OCl$: C, 69.07; H, 6.28. Found: C, 68.91; H, 6.25.

2-(1-Methylindol-3-yl)-3-methylcyclohexanone (**2.2p**).

Hexanes:diethyl ether (4:1) was used as the eluent to give a colorless thick oil as a mixture of *cis* and *trans* isomers in a ratio of 1.35:1 (signals for *trans* isomer in square brackets): ^{1}H NMR δ 0.81 [0.87] (d, *J* =7.1 [7.2] Hz, 3H), 1.83-2.58 (m, 7H), 3.70 [3.73] (s, 3H), 4.25 [3.45] (d, *J* = 4.8 [11.2] Hz, 1H), 6.86 [7.35] (s, 1H), 7.04–7.28 (m, 3H), 7.53 [7.40] (d, *J* = 7.8 Hz, 1H); ^{13}C NMR δ 15.3 [21.5], 23.7 [25.9], 31.2 [29.6], 34.2 [32.6], 38.1 [40.6], 41.1 [41.6], 52.6 [56.0], 109.0 [109.2], 110.5, 118.5 [118.6], 119.4, 121.2 [121.3], 127.9 [127.5], 128.0, 136.1 [136.9], 210.6 [210.5]; HRMS Calcd for $C_{16}H_{19}NO$: 242.1545 (M+1), Found: 242.1517.

2-(5-Methylthien-2-yl)-3-methylcyclohexanone (**2.2q**).

Hexanes:diethyl ether (10:1) was used as the eluent to give a colorless oil in *trans* form: ^{1}H NMR δ 0.94 (d, *J* = 6.2 Hz, 3H), 1.55–2.13 (m, 5H), 2.34–2.56 (m, 2H), 2.46 (s, 3H), 3.44 (d, *J* = 7.8 Hz, 1H), 6.55 (d, *J* = 3.3 Hz, 1H), 6.60 (m, 1H); ^{13}C NMR δ 15.2, 21.1, 25.6, 33.9, 41.4, 41.7, 59.8, 124.4, 125.9, 137.4, 138.8, 208.8; HRMS Calcd for $C_{12}H_{16}OS$: 209.1000 (M+1), Found: 209.1018.

3-Methyl-2-(1-methylindol-3-yl)cycloheptanone (**2.2r**) and 2-Methyl-7-(1-methylindol-3-yl)cycloheptanone (**2.3r**).

Hexanes:ethyl acetate (20:1) was used as the eluent to give pure *cis*- and *trans*-**2t** and *trans*–**3t**. *cis*–**2t**: yellowish oil, yield (68%): ^{1}H NMR δ 0.87 (d, *J* = 7.2 Hz, 3H), 1.50–1.64 (m, 1H), 1.83–2.00 (m, 5H), 2.33–2.50 (m, 2H), 2.68 (dt, *J* = 17.2 and 4.9 Hz, 1H), 3.78 (s, 3H), 4.56 (d, *J* = 2.5 Hz, 1H), 7.06–7.12 (m, 1H), 7.18–7.31 (m, 2H), 7.43 (s, 1H), 7.46 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR δ 15.3, 24.1, 24.3, 32.6, 35.7, 37.0, 44.4, 51.7, 109.1, 111.9, 118.1, 118.6, 121.3, 127.6, 127.8, 136.2, 212.5; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.77; H, 8.47; N, 5.26. *trans*-**2t**: white plates, mp 86–87 °C, yield (13%): ^{1}H NMR δ 1.00 (d, *J* = 6.7 Hz, 3H), 1.32–1.67 (m, 3H), 1.80–2.02 (m, 3H), 2.14–2.26 (m, 2H), 2.78–2.86 (m, 1H), 3.58 (d, *J* = 10.5 Hz, 1H), 3.77 (s, 3H), 7.04 (s, 1H), 7.10–7.15 (m, 1H), 7.19–7.29 (m,

2H), 7.72 (dd, J = 7.7 and 1.2 Hz, 1H); ^{13}C NMR δ 21.7, 27.5, 29.6, 32.8, 36.1, 36.6, 40.1, 59.0, 109.1, 112.0, 119.2, 119.8, 121.9, 126.0, 127.8, 137.0, 212.1; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.98; H, 8.47; N, 5.40. *trans*-**3t**: white plates, mp 83–84 °C, yield (3%): ^{1}H NMR δ 1.11 (d, J = 6.7 Hz, 3H), 1.42–1.92 (m, 6H), 2.02–2.21 (m, 2H), 2.91–3.00 (m, 1H), 3.76 (s, 3H), 4.32 (dd, J = 9.7 and 4.2 Hz, 1H), 7.06–7.11 (m, 1H), 7.16 (s, 1H), 7.17–7.30 (m, 2H), 7.48 (d, J = 7.9 Hz, 1H); ^{13}C NMR δ 16.3, 25.4, 28.2, 32.5, 32.7, 33.2, 46.0, 47.9, 109.2, 113.9, 118.5, 118.7, 121.4, 127.0, 127.2, 136.6, 214.9; Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 79.56; H, 8.61; N, 5.29.

3-Methyl-2-(5-methylthien-2-yl)cycloheptanone (**2,2s**).

Hexanes:diethyl ether (10:1) was used as the eluent to give pure *cis* and *trans* isomers. *cis* Isomer: colorless oil, yield (55%): ^{1}H NMR δ 0.92 (d, J = 7.2 Hz, 3H), 1.50–1.65 (m, 1H), 1.72–1.90 (m, 5H), 2.25–2.35 (m, 1H), 2.40–2.50 (m, 1H), 2.45 (s, 3H), 2.65 (dt, J = 17.2 and 5.0 Hz, 1H), 4.35 (d, J = 2.8 Hz, 1H), 6.58–6.60 (m, 1H), 6.68 (d, J = 3.6 Hz, 1H); ^{13}C NMR δ 15.0, 16.2, 23.8, 24.8, 36.2, 37.0, 43.5, 56.8, 123.8, 125.4, 138.5 (2C), 210.7; HRMS Calcd for $C_{13}H_{18}OS$: 222.1078 Found: 222.1074. *trans* Isomer: colorless oil, yield (11%): ^{1}H NMR δ 0.98 (d, J = 6.7 Hz, 3H), 1.26–1.31 (m, 1H), 1.51–1.58 (m, 2H), 1.77–2.03 (m, 4H), 2.30–2.36 (m, 1H), 2.43 (s, 3H), 2.77–2.85 (m, 1H), 3.40 (d, J = 10.7 Hz, 1H), 6.69 (m, 1H), 6.70 (d, J = 3.3 Hz, 1H); ^{13}C NMR 15.2, 21.4, 27.2, 29.2, 36.4, 37.9, 40.4, 62.9, 124.9, 125.1, 138.6, 138.8, 211.1; Anal. Calcd for $C_{13}H_{18}OS$: C, 70.23; H, 8.16. Found: C, 70.11; H, 8.41.

2-((*E*)-2-Phenylethenyl)cycloheptanone (**2t**).

Hexanes:diethyl ether (6:1) was used as the eluent to give a colorless oil: ^{1}H NMR δ 1.37–1.99 (m, 8 H), 2.49–2.56 (m, 2H), 3.28–3.35 (m, 1 H), 6.30 (dd, J = 16.0 and 7.1 Hz, 1H), 6.40 (d, J = 16.0 Hz, 1H), 7.19-7.35 (m, 5H); ^{13}C NMR δ 24.7, 27.8, 29.5, 31.4, 42.3, 56.1, 126.1, 127.2, 128.4, 128.5, 130.7, 137.0, 213.4; Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.90; H, 8.54.

2.4.6. Preparation of 2-(Benzotriazol-1-yl)-2-(4-methoxyphenyl)-1-(4-methylphenyl)ethanol (**11**).

To a solution of 1-(4-methoxybenzyl)benzotriazole (**1e**) (0.239 g, 1 mmol) in THF (30 mL) at –78 °C under argon was added dropwise *n*-BuLi (2.2 *M* , 0.5 mL, 1.1 mmol). After 30 min, *p*-tolualdehyde (0.13 mL, 1 mmol) in THF (10 mL) was added. The mixture was stirred at –78 °C for an additional 4 h and allowed to warm to rt overnight. A saturated aqueous NH_4Cl solution (30 mL) was added, and the mixture was extracted with diethyl ether (3 x 50 mL). The combined organic layer was washed with brine, dried ($MgSO_4$) and solvent was removed under vacuum. The remaining oil was subjected to column chromatography (hexane:ether=1:1) to give *threo* (0.155 g, 42%) as the first fraction and *erythro* (0.075 g, 21%) as the second fraction. *threo*: mp 146–147 °C; ^{1}H NMR δ 2.28 (s, 3H), 3.69 (s, 3H), 3.88 (d, J = 4.4 Hz, 1H), 5.75 (d, J = 8.7 Hz, 1H), 5.89 (dd, J = 8.6 and 4.1 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 6.98 (d, J = 8.8 Hz, 2H), 7.03 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.28–7.37 (m, 3H), 8.01–8.04 (m, 1H); ^{13}C NMR δ 21.1, 55.1, 70.0, 76.2, 110.0, 113.9, 119.8, 124.2, 126.9, 126.9, 127.5, 128.2, 128.9, 133.5, 136.4, 137.7, 145.8, 159.4; Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89, N, 11.69. Found: C, 73.54, H; 5.85 N, 11.76. *erythro*: mp 86–87 °C, ^{1}H NMR δ 2.28 (s, 3H), 3.69 (m, 1H), 3.75 (s, 3H), 5.69 (d, J = 5.4 Hz, 1H), 5.98 (m, 1H), 6.79 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.0 Hz, 2H), 7.09–7.32 (m, 7H), 8.00 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 21.1, 55.2, 68.7, 75.0, 109.7, 113.7, 119.8, 124.1, 126.5, 126.7, 127.4, 128.8, 129.9, 132.9, 136.5, 137.7, 145.4, 159.4; Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89, N, 11.69. Found: C, 73.64, H; 5.97, N, 11.88.

CHAPTER 3
PETERSON OLEFINATION WITH BENZOTRIAZOLE STABILIZED ANIONS

3.1 Introduction

Benzotriazole has a appreciable activating effect towards proton loss of a Csp^3–H bond situated in the α-position (for reviews see [95S1315, 91T2683]). Silicon shows a similar behaviour but – as is sometimes the case with benzotriazole – this activating effect alone is not significant enough to make it practical. Additional activation is needed and this is usually accomplished by an additional activating group: phenyl, thiane, ether, halogen etc. Unlike silanes which are not easily accessible, benzotriazole derivatives are easily obtained by a wide variety of methods. One of the most powerful transformations mediated by silicon is Peterson olefination [90OR(38)1]. It is now shown that when this reaction is used with certain benzotriazolyl derivatives containing silicon, an important homologation reaction occurs.

3.2 Efficient Transformations of Aldehydes and Ketones into One-Carbon Homologated Carboxylic Acids

Synthetic transformations of carbonyl compounds **3.1** into one-carbon homologated carboxylic acids **3.4** (Figure 3.1) are of great importance, as evidenced by the volume of literature on this subject [49JOC1013, 67TL3201, 68AG(E)391, 72AG(E)391, 71TL871, 72JCS(CC)526, 76JOC564, 77JA182, 82SC415, 82T139, 83JOC3566, 83S1043, 86S645]. The most important and most commonly used methods for the transformation **3.1**→**3.4** rely on the hydrolysis of intermediates of type **3.2** as

shown by the following classification: (i) α-Acetoxyacrylonitriles (**3.2**, X = OAc, Y = CN) are prepared from the reactions of diethyl *t*-butoxy(cyano)methylphosphonate $(EtO)_2POCH(CN)OBu^t$ with aldehydes and ketones, followed by the replacement of the

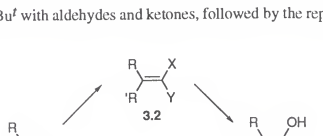


Figure 3.1

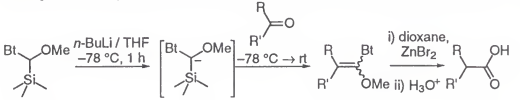
tert-butyl group by the acetyl group [77JA182], or from the reaction of chloroacetonitrile with ketones, followed by the treatment with dry HCl and acetic anhydride [74JCS(CC)988]. However, both processes require three steps for the transformations of ketones to acids and involve manipulation of toxic cyanides. (ii) α-Cyanoenamines (**3.2**, X = PhNMe or NMe_2, Y = CN) are obtained from the reactions of α-(*N*-methylanilino)acetonitrile [83JOC3566] or $Me_2NCH(CN)PO(OEt)_2$ [82T139] with carbonyl compounds. However, this method may not be general for ketones, for which benzophenone [74JCS(CC)988] and acetophenone [82T139] are the only examples reported. Moreover, the transformation **3.1**→**3.4** requires two steps. (iii) α–Cyanoenamides (**3.2**, X = ArCONMe, Y = CN) are produced from α-(*N*-aroyl-*N*-methylamino)acetonitriles and carbonyl compounds [83S1043]. However, this approach is apparently limited to aromatic aldehydes. (iv) α-Phosphonoenamines (**3.2**, X = $PO(OEt)_2$, Y = NMe_2) are prepared from *N*,*N*-dimethylaminomethylenediphosphonate $Me_2NCH[PO(OEt)_2]_2$ and aldehydes [68AGE391, 82SC415]. However, the reported yields from application of this method to non-conjugated aldehydes are less than 35% [82SC415]. (v) 1-Formylamino-1-sulfonylalkenes (**3.2**, X = NHCHO, Y = SO_2Ar) are

obtained from the reactions of aldehydes and ketones with isocyanomethyl aryl sulfones $CNCH_2SO_2Ar$ [72AG(E)311]. However, two steps are required to transform **3.1**→**3.4** in overall yields of 35-50%. (vi) Ketene thioacetals (**3.2**, X, Y = $S(CH_2)_3S$) are prepared from the reactions of 2-trimethylsilyl-1,3-dithiane[72JCS(CC)526] or 1,3-dithiacyclohexylidinetrimethoxy phosphorane [67TL3201] with aldehydes and ketones. However, effective hydrolysis for these approaches involves the use of mercury salts. (vii) Ketene-O,S-acetals (**3.2**, X = OMe, Y = Sph) [84TL3539, 86JOC879], produced from the Peterson olefination of methoxyphenylthiotrimethylsilylmethane with aldehydes and ketones, are readily converted into thioesters on treatment with TMS-Cl, NaI or with LiSMe. This strategy is of potential utility for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids.

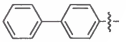
Alternative approaches for the transformation **3.1**→**3.4** involve the intermediates **3.3** (Figure 3.1) from the addition of cyanide to carbonyl compounds. Accordingly, aldehydes or methyl aryl ketones react with cyanide, followed by *o*-acetylation, deacetoxylation by catalytic hydrogenation, and hydrolysis of the cyano group to afford one-carbon homologated carboxylic acids [49JOC1013, 76JOC564, 86S645]. Yet other routes are *via* cyanoepoxides [74JCS(CC)988]. However, these processes are multistep and use cyanides.

The utility of alkoxy(benzotriazol-1-yl)methanes as versatile one-carbon homologation reagents has recently been demonstrated [94AA31, 95TL841, 95JA12015]. Their silylated derivatives, trimethylsilyl(alkoxy)benzotriazol-1-ylmethanes have been used by Johnson *et al.* in facile syntheses of oxindoles *via* Peterson olefination and photolysis [94H1913, 95TL6321]. We have now developed trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) and demonstrated that it provides a convenient method for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids.

Trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) was easily prepared in 75% yield as a crystalline solid by the previously reported method [91JCS(P1)3295].



3.5 **3.6** **3.7** **3.4**

3.4	R	R'
a	Me	Ph
b	Et	Ph
c	Me	4-$MeOC_6H_4$
d	Ph	4-BrC_6H_4
e		$-C_5H_{10}-$
f	H	
g	H	4-(*n*-$C_6H_{13}O)C_6H_4$
h	H	
i	H	4-MeC_6H_4
j	H	
k	H	Ph(Me)CH

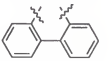
3.7	R	R'
a	Me	Ph
b		

Figure 3.2

The lithiation of **3.5** occurred readily with *n*-butyllithium at –78 °C to give a deep blue solution of the anion **3.6**, which underwent Peterson olefination reactions with acetophenone and fluorenone to give 1-(1-methoxy-1-alkenyl)benzotriazoles **3.7a** and **3.7b** in 76% and 81% yield respectively. Compound **3.7a** was obtained as a mixture of *cis*- and *trans*-isomers (Figure 3.2). The 1-(1-methoxy-1-alkenyl)benzotriazole is an acyl benzotriazole synthon in which the carbonyl group is masked as an enol ether. Accordingly, transformation of **3.7** into carboxylic acids was readily achieved in excellent

yield by treatment with zinc bromide and hydrochloric acid in refluxing 1,4-dioxane, as exemplified by the conversion of **3.7a** into the corresponding acid **3.4a**. Conveniently, it is not necessary to separate the intermediates **3.7** for the preparation of carboxylic acids **3.4**. Thus, trimethylsilyl(methoxy)benzotriazol-1-ylmethyl anion **3.6** was treated with a variety of aldehydes and ketones (Figure 3.2), and the resulting crude intermediates **3.7** were subjected to hydrolysis with hydrochloric acid in the presence of zinc bromide to provide the corresponding one-carbon homologated acids **3.4b-k** in 45-57% overall yields from the starting aldehydes and ketones. By-product benzotriazole was easily removed due to its lower acidity (see experimental section). As shown in Figure 3.2, this approach works well with both aliphatic and aromatic aldehydes and aryl aryl, aryl alkyl and alkyl alkyl ketones, demonstrating its wide generality. 1-(1-Methoxy-1-alkenyl)benzotriazoles **3.7a** and **3.7b**, and carboxylic acids **3.4a-k** all showed the expected ^{1}H and ^{13}C spectra and all new compounds were further characterized by their elemental analyses.

In summary, trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) is an advantageous reagent for the transformation of aldehydes and ketones into one-carbon homologated carboxylic acids in light of the generality of the method, the ready availability of the starting materials and the simplicity of the experimental procedure.

3.3 Experimental Section

General Methods. Melting points were determined with a hot-stage apparatus and are uncorrected. NMR spectra were recorded using $CDCl_3$ as the solvent with tetramethylsilane as the internal standard for ^{1}H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately prior to use from sodium/benzophenone. All reactions with air-sensitive compounds were carried out under an argon atmosphere. Column chromatography was conducted with silica gel

230–400 mesh. Trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) was prepared according to our reported procedure [91JCS(P1)3295].

General Procedure for the Preparation of 1-(Benzotriazol-1-yl)-1-methoxy-1-alkene **3.7a** and **3.7b**

To a solution of trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) (1.17 g, 5 mmol) in THF (70 mL) at –78 °C under argon was added *n*-BuLi (2.9 mL, 5.7 mmol, 2 *M* in cyclohexane). After 1 h, the appropriate ketone (5.7 mmol) in THF (8 mL) was added. The mixture was stirred at –78 °C for an additional hour and warmed to room temperature overnight. Saturated aqueous NH_4Cl (70 mL) was added and the mixture extracted with ethyl ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude material was purified by column chromatography.

1-(Benzotriazol-1-yl)-1-methoxy-2-phenyl-1-propene (**3.7a**).

Hexane:ethyl ether (4:1) as eluent gave a mixture of *cis*- and *trans*-isomers (1.15 g , 76%). For characterization purpose, this oil mixture was recrystallized from hexane : ethyl ether to give *trans*-isomer: yield: 0.46 g (35%); mp 101–102 °C: ^{1}H NMR δ 2.35 (s, 3 H), 3.41 (s, 3H), 6.91–6.99 (m, 5H), 7.25–7.30 (m, 1H), 7.35–7.37 (m, 2H), 7.96 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 17.5, 57.0, 110.0, 119.7, 120.0, 124.0, 127.0, 127.2, 128.0, 128.1, 133.2, 137.9, 139.3, 144.9. Calcd for $C_{16}H_{15}N_3O$: C, 72.42; H, 5.70; N, 15.84. Found: C, 72.41; H, 5.59; N, 16.02.

Fluorenylidene(methoxy)(benzotriazol-1-yl)methane (**3.7b**).

Hexane:ethyl ether (3:1) as eluent (1.1 g, 81%), mp 134-136 °C: ^{1}H NMR δ 3.59 (s, 3H), 5.50 (d, *J* = 7.9 Hz, 1H), 6.78 (t, *J* = 7.6 Hz, 1H), 7.18 (t, *J* = 6.6 Hz, 1H), 7.40–7.55 (m, 5H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.75–7.78 (m, 1H), 8.24–8.29 (m, 2H);

^{13}C NMR δ 56.3, 110.2, 118.3, 119.6, 119.7, 120.4, 122.4, 125.1, 125.5, 127.0, 127.4, 127.7, 128.4, 129.4, 133.1, 134.6, 136.1, 139.6, 139.7, 140.7, 145.5. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.91. Found: C, 77.53; H, 4.49; N, 12.94.

Preparation of 2-Phenylpropionic Acid **3.4a** from Intermediate Product **3.7a**.

To a solution of 1-(benzotriazol-1-yl)-1-methoxy-2-phenyl-1-propene (**3.7a**) (0.26 g, 1 mmol) in dry 1,4-dioxane (5 mL) under argon was added zinc bromide (0.56 g, 2.5 mmol). After the mixture was refluxed for 1 h, aqueous hydrochloric acid (1 mL, 6 *N*) was added. The mixture was further refluxed for 4 h. The solvent was evaporated at reduced pressure and water (20 mL) was added to the residue. The mixture was extracted with ethyl ether (3 × 20 mL). The combined organic layer was extracted with aqueous $NaHCO_3$ (3 × 20 mL, 5%). The aqueous layer was acidified with HCl (6 *N*) to pH = 4 and extracted with ethyl ether (3 × 20 mL). The combined organic layer was washed with water (20 mL), dried ($MgSO_4$) and evaporated to give the pure oil (Lit. [54JA5364] bp 177 °C / 44 mm); yield: 0.12 g (80%): ^1H NMR δ 1.50 (d, *J* = 7.2 Hz, 3H), 3.73 (q, *J* = 7.2 Hz, 1H), 7.25–7.32 (m, 5H), 12.01 (br s, 1H); ^{13}C NMR δ 18.1, 45.4, 127.4, 127.6, 128.7, 139.7, 180.9.

General Procedure for the Preparation of Carboxylic Acids **3.4b-h** from Aldehydes and Ketones.

To a solution of trimethylsilyl(methoxy)benzotriazol-1-ylmethane (**3.5**) (1.17 g, 5 mmol) in THF (70 mL) at –78 °C under argon was added *n*-BuLi (2.9 mL, 5.7 mmol, 2 M in cyclohexane). After 1 h, the appropriate ketone or aldehyde (5.7 mmol) in THF (8 mL) was added. The mixture was stirred at –78 °C for an additional hour and warmed to r.t. overnight. Saturated aqueous NH_4Cl (70 mL) was added and the mixture extracted with ethyl ether (3 × 50 mL). The combined organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude solution was filtered through a plug of

silica gel. The ether was removed from the filtrate and the residue dissolved in dry 1,4-dioxane (20 mL). To this solution under argon was added zinc bromide (1.42 g, 6.3 mmol). After the mixture was refluxed for 1 h, aqueous hydrochloric acid (2.5 mL, 6 *N*) was added. The mixture was further refluxed for 4 h. The solvent was evaporated at reduced pressure and water (50 mL) was added to the residue. The mixture was extracted with ether (3 × 50 mL). The combined organic layer was extracted with aqueous $NaHCO_3$ (3 × 50 mL, 5%). The aqueous layer was acidified with HCl (6 *N*) to pH = 4 and extracted with Et_2O (3 × 50 mL). The combined organic layer was washed with water (60 mL), dried ($MgSO_4$) and evaporated to give the pure product.

2-Phenylbutyric Acid (**3**, **4b**).

Colorless solid; yield: 0.45 g (55%); mp 39–42 °C (Lit. [54JA3036] mp 42–43 °C): ^{1}H NMR δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.73–1.88 (m, 1H), 2.03–2.17 (m, 1H), 3.45 (t, *J* = 7.7 Hz, 1H), 7.22–7.32 (m, 5H), 10.98 (br s, 1H). ^{13}C NMR δ 12.1, 26.3, 53.4, 127.4, 128.1, 128.6, 138.3, 180.5.

2-(4-Methoxyphenyl)propionic Acid (**3**, **4c**).

Colorless solid; yield: 0.48 g (53%); mp 54–56 °C (Lit. [64AJC379] mp 56–57 °C): ^{1}H NMR δ 1.48 (d, *J* = 7.2 Hz, 3H), 3.68 (q, *J* = 7.2 Hz, 1H), 3.77 (s, 3H), 6.85 (d, *J* = 8.6 Hz, 2H), 7.23 (d, *J* = 8.6 Hz, 2H), 10.50 (br s, 1H); ^{13}C NMR δ 18.1, 44.5, 55.2, 114.0, 128.6, 131.9, 158.8, 181.0.

(4-Bromophenyl)phenylacetic Acid (**3**, **4d**).

Colorless solid; yield: 0.63 g (43%); mp 118–120 °C (Lit. [60JCS372] mp 120–121°C): ^{1}H NMR δ 4.99 (s, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.28–7.33 (m, 5H), 7.44 (d, *J* = 8.5 Hz, 2H), 11.38 (br s, 1H); ^{13}C NMR δ 56.4, 121.6, 127.7, 128.5, 128.8, 130.4, 131.7, 136.8, 137.3, 178.5.

Cyclohexylformic Acid (**3.4e**).

Colorless oil (Lit. [57JOC1680] bp 63–67 °C / 1 mm); yield: 0.36 g (55%): ^{1}H NMR δ 1.20–1.96 (m, 10H), 2.28–2.38 (m, 1H), 11.83 (br s, 1H); ^{13}C NMR δ 25.2, 25.6, 28.7, 42.9, 182.7.

3,4-Methylenedioxyphenylacetic Acid (**3.4f**).

Colorless solid; yield: 0.51 g (57%); mp 125–127 °C (Lit. [08CB2751] mp 127 °C): ^{1}H NMR δ 3.55 (s, 2H), 5.94 (s, 2H), 6.69–6.77 (m, 3H) (OH signal was not detected); ^{13}C NMR δ 42.2, 102.7, 109.9, 111.4, 124.1, 128.3, 148.5, 149.4, 179.4.

4-Hexyloxyphenylacetic Acid (**3.4g**).

Colorless solid; yield: 0.53 g (45%); mp 80–81 °C (Lit. [80CCC1401] mp 77–78.5 °C): ^{1}H NMR δ 0.90 (t, J = 6.8 Hz, 3H), 1.29–1.35 (m, 4H), 1.40–1.50 (m, 2H), 1.71–1.81 (m, 2H), 3.57 (s, 2H), 3.93 (t, J = 6.6 Hz, 2H), 6.85 (d, J = 8.7 Hz, 2H), 7.17 (d, J = 8.7 Hz, 2H), 9.85 (br s, 1H); ^{13}C NMR NMR δ 15.6, 24.2, 27.3, 30.8, 33.2, 41.8, 69.6, 116.3, 126.7, 131.9, 160.0, 179.9.

4-Phenylphenylacetic Acid (**3.4h**).

Colorless solid; yield: 0.48 g (45%); mp 162–164 °C (Lit. [46JOC798] mp 153 °C): ^{1}H NMR δ 3.70 (s, 2H), 7.34–7.46 (m, 5H), 7.55–7.59 (m, 4H), 10.40 (br s, 1H). ^{13}C NMR δ 40.7, 127.1, 127.3, 127.4, 128.8, 129.8, 132.2, 140.4, 140.7, 177.8. Calcd for $C_{14}H_{12}O_2$: C, 79.23; H, 5.70. Found: C, 79.02; H, 5.78.

4-Methylphenylacetic Acid (**3.4i**).

Colorless solid; yield: 0.42 g (56%); mp 90–92 °C (Lit. [48JOC763] mp 87–91.5 °C): ^{1}H NMR δ 2.33 (s, 3H), 3.60 (s, 2H), 7.11-7.18 (m, 4H), 10.62 (br s, 1H); ^{13}C NMR δ 21.0, 40.6, 129.2, 129.3, 130.2, 137.0, 178.2.

1-Naphthylacetic Acid (**4j**).

Colorless solid; yield: 0.53 g (57%); mp 130–132 °C (Lit. [50JA4302] mp 132 °C): ^{1}H NMR δ 4.07 (s, 2H), 7.38–7.55 (m, 4H), 7.78–7.87 (m, 2H), 7.95 (d, J = 8.9

Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR δ 38.7, 123.6, 125.4, 125.8, 126.5, 128.2, 128.3, 128.7, 129.7, 132.0, 133.8, 178.1.

3-Phenylbutanoic Acid (**3.4k**).

Colorless oil (Lit. [55JCS3919] bp 142 °C / 1 mm); yield: 0.44 g (54%). ^{1}H NMR δ 1.33 (d, *J* = 7.0 Hz, 3H), 2.55–2.73 (m, 2H), 3.22–3.34 (m, 1H), 7.22–7.35 (m, 5H), 11.31 (br s, 1H). ^{13}C NMR δ 21.8, 36.1, 42.6, 126.5, 126.7, 128.5, 145.4, 178.8.

CHAPTER 4
MASKED ALPHA-ARYLALKENYLLITHIUM REAGENTS FOR SYNTHESES OF FUNCTIONALIZED MONOSUBSTITUTED AND 1,1-DISUBSTITUTED ETHYLENES

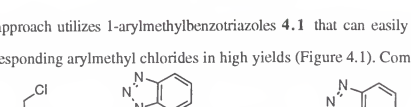
4.1 Introduction

Due to its ability to favor α-carbanion formation, benzotriazole has proven to be a good tool for the introduction of silicon into organic molecules [87JCS(P1)819, 90HAC21, 96S1425] (see also Chapter 3). The potentially powerful transformations attributed to the presence of silicon in organic molecules thus become available. One of the most useful transformations in this category is the formation of an alkene by vicinal elimination of silicon (for comprehensive reviews of these types of reactions see refs [90MI1, 91COS(6)1000, 95COG(1)648]). Herein is presented a versatile method for the introduction of 1-arylethenyl moieties into organic molecules by the vicinal elimination of silicon from 2-benzotriazolylethylsilanes. These intermediates act as masked 1-arylethenyl units that can be transformed into the corresponding alkene when needed (cf. the concept of "silicon-masked enones" introduced by Fleming [78JCS(CC)176, 78JCS(CC)177]). The vicinal elimination of silicon can be accomplished by several protocols including: pyrolysis, [1,4]-Brook rearrangement, and fluoride ion induced β-elimination. Examples are documented illustrating potentially general methods for the preparation of styrenes, 1,2-disubstituted allyl alcohols, α-substituted acrylamides, 1,3-disubstituted homoallyl alcohols, and γ,δ-unsaturated ketones.

Previous methods for generating alkenyllithiums use either the Shapiro reaction applied to carbonyl compounds [80TL3849, 90OR(39)1] or lithium-halogen exchange applied to the corresponding vinyl halides [88MI1].

4.2 Results and Discussion

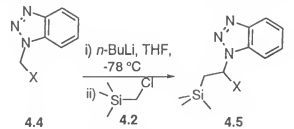
This approach utilizes 1-arylmethylbenzotriazoles **4.1** that can easily be prepared from the corresponding arylmethyl chlorides in high yields (Figure 4.1). Compounds **4.1**



Entry	a	b	c	d	e	f
X	2-CH_3	4-CH_3	2-Cl	2-Cl-6-F	4-F	2-F
Yield % **4.1**	89	92	98	94	78	87
Yield % **4.3**	88	90	93	89	96	92

Figure 4.1

can be deprotonated to give the corresponding benzyllithiums and reacted with electrophiles in high yields (for leading examples see [95JA12015, 96JOC7571]). The nucleophilic



Entry	a	b	c	d	e	f
X	H	OMe	OPh	O NEt_2	SPh	$SiMe_3$
Yield % **4.5**	85	72	87	93	74	89

Figure 4.2

displacement of chlorine in chloromethyltrimethylsilane **4.2** by the carbanion derived from **4.1** gives rise to reagents **4.3a–f** in high yields (Figure 4.1). This reaction works equally well with substrates **4.4** where the aryl group in **4.1** is replaced by a heteroatom or hydrogen (Figure 4.2). Reagents **4.5a-f** were obtained in excellent yields (Figure 4.2). These reagents **4.3a-f** and **4.5a-f** are highly stable compounds which can be distilled under reduced pressure without decomposition.

The vicinal elimination of silicon in compounds **4.3** can be accomplished by treatment with fluoride ion. Both tetrabutylammonium fluoride (TBAF) 1 *M* solution in THF and cesium fluoride in dimethylformamide work well with **4.3d** to give the corresponding styrene **4.8** (Figure 4.3) in high yield. The main reason why TBAF shows higher elimination rate is the higher concentration of "naked" fluoride ion (for recent discussion see [90JA7619] and references therein). 18-Crown-6 was used to increase the solubility of cesium fluoride in DMF [84TAL1036]. However, the elimination rate is still slow compared to that with TBAF.

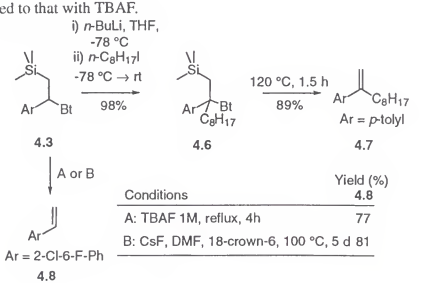
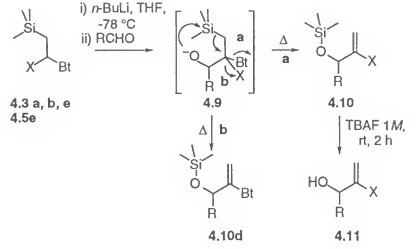


Figure 4.3

The most useful feature of reagents **4.3** is that when are treated with *n*-BuLi, the deprotonation occurs regiospecifically in the alpha position to the benzotriazole. The corresponding anions react with electrophiles to give the corresponding adducts. Thus,

compounds of type **4.6** are cleanly obtained with alkyl halides (Figure 4.3). Heating these adducts at 120 °C affords the corresponding 1,1-disubstituted ethylenes in excellent yields as illustrated by the transformation **4.6** → **4.7** (Figure 4.3).

Addition of the carbanions derived from **4.3** or **4.5e** to non-enolizable aldehydes is a facile process. Aryl- and tertiary alkyl-aldehydes gave trimethylsilylallyl ethers by a [1,4]-Brook rearrangement [80MI1, 85TL4471] (Figure 4.4). This process is most likely intramolecular since the stereochemistry of the intermediate alkoxides **4.9** dramatically influences the reaction conditions required. Thus, when the phenyl group of the incoming nucleophile possesses no substituents in the 2- or 6-position, the rearrangement of the



	X	R	Yield (%)
4.10a	4-MeC_6H_4	3-$MeOC_6H_4$	72
4.10b	4-MeC_6H_4	*t*-Bu	87
4.10c	4-FC_6H_4	3-$MeOC_6H_4$	52
4.10d	Bt	C_6H_5	70
4.10e, 4.11	2-MeC_6H_4	3-$MeOC_6H_4$	70

Figure 4.4

alkoxide **4.9** takes place on simple warming from –78 °C to rt as is the case with compounds **4.10a-d** (Figure 4.4). In case of **4.5e**, the phenylthio group acts as a better

leaving group than benzotriazole, consequently the benzotriazolyl moiety is retained in the allylic ether **4.10d**. In the case of **4.3a**, heating the alkoxide **4.9** under reflux for 3 h was necessary to yield the corresponding **4.10e**. Upon treatment of **4.10e** with TBAF the free allyl alcohol **4.11** was isolated in high yield (Figure 4.5). The reaction of **4.3b** with phenyl isocyanate gave the intermediate alkoxide **4.10** which upon aqueous work-up afforded the corresponding masked acrylamide **4.12** in excellent yield (Figure 4.5). Attempted vicinal elimination of silicon in **4.12** with TBAF afforded only the desilylation product **4.13** probably due to the proximity of the acidic amide proton. However, direct heating of intermediate **4.10** neat at 130 °C, gave the acrylamide **4.11** in good yield (Figure 4.5). To our best knowledge, such a silicon [1,4]-C→O rearrangement in amide systems is unprecedented.

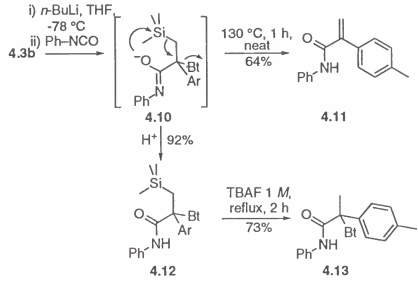


Figure 4.5

Phenyloxirane reacts with the carbanion derived from **4.3c** to give the intermediate **4.14** which did not rearrange to the corresponding homoallylic alcohols by a [1,5]-Brook rearrangement on refluxing in THF. The adduct **4.15** was obtained in high yield upon aqueous work-up of **4.14** (Figure 4.6). To accomplish the vicinal elimination of silicon,

alcohol **4.15** was first deprotonated and then treated with TBAF, to afford the desired elimination product **4.16** in high yield (Figure 4.6).

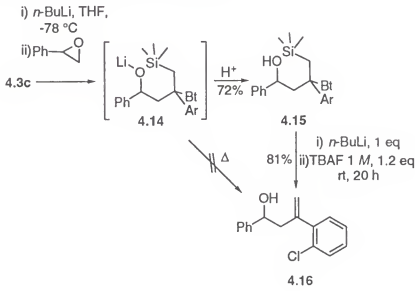


Figure 4.5

Conjugate addition of alkenyllithiums is usually accomplished *via* previous conversion into the cuprate. This was not needed in our case, as deprotonation of **4.3b** with *n*-BuLi and subsequent reaction with an enone gave regiospecifically the conjugate addition product **4.17** in high yield (Figure 4.6). The final elimination is accomplished with TBAF to convert **4.17** into the γ,δ-unsaturated ketone **4.18** in high yield.

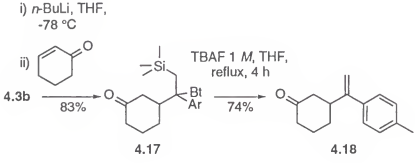


Figure 4.7

To synthesize enones we needed to react the anion derived from **4.3b** with a carboxylic acid derivative. Esters gave complex mixtures, but acid chloride afforded the adduct **4.19** in excellent yield. The only reaction conditions we found to accomplish the

elimination from these substrates are CsF in DMF and a crown ether to enhance the solubility of the fluoride. These conditions afforded a mixture of the desired enone **4.20** in high yield but also the chalcone **4.21** as the *E*–regioisomer (Figure 4.8). The formation of compound **4.21** can be explained by a Grovenstein-Zimmerman rearrangement [78AG(E)313, 80MI2]: the intermediate carbanion **4.22** is stabilized by formation of the

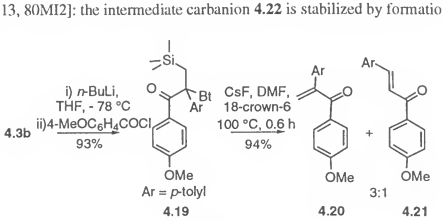


Figure 4.8

bridged phenonium anion **4.23** in which the geometry of the bonding is favorable to the elimination of the benzotriazole, concomitant with the formation of a hydroxyallene **4.24** that tautomerizes to the (*E*)-chalcone **4.21** (Figure 4.9).

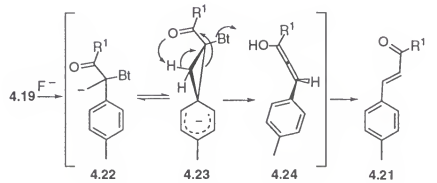


Figure 4.9

In summary, we have shown that reagents of type **4.3** and **4.5** are excellent for the regiospecific preparation of compounds containing a silicon-masked α-aryl-alkenyl moiety.

These compounds can eliminate the protecting group under a variety of conditions to give the corresponding terminal alkene containing compounds.

4.3 Experimental Section

General Methods. Melting points were determined with a MEL-TEMP capillary melting point apparatus equipped with a Fluke 51 digital thermometer. NMR spectra were taken in $CDCl_3$ with tetramethylsilane as internal standard for ^1H (300 MHz) or solvent as internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately before use from sodium / benzophenone. Tetrabutylammonium fluoride (TBAF) 1*M* solution in tetrahydrofuran was stored over 4 Å molecular sieves. Chloromethyltrimethylsilane was purchased from Gelest, Inc. Column chromatography was conducted with silica gel grade 230-400 mesh. All organometallic reactions were carried out under Ar in oven-dried glassware. All other reagents are reagent grade and were used without purification.

4.3.1 General Procedure for the Synthesis of Compounds **4.1a-f.**

A mixture of benzotriazole (7.743 g, 65 mmol) and the corresponding benzyl chloride (50 mmol) in toluene (40 mL) was refluxed for 24 h. After the toluene was distilled off under reduced pressure, aqueous sodium hydroxide (5%, 50 mL) and dichloromethane (100 mL) were added. The organic layer was separated, washed with aqueous sodium hydroxide (2 × 50 mL), water (2 × 50 mL) and dried ($MgSO_4$). After the solvent was removed, the residue was recrystallized from the appropriate solvent to give the pure product.

1-(2-Methylbenzyl)-1*H*-benzotriazole **4.1a.**

Colorless prisms (88 %), mp 79.5-80.7 °C (diethyl ether) (lit [56JCS1076] mp 84-85 °C): ^1H NMR δ 2.33 (s, 3H), 5.84 (s, 2H), 7.04 (d, *J* = 7.4 Hz, 1H), 7.12-7.40 (m, 6H), 8.05 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 19.2, 50.7, 109.8, 120.0,

123.8, 126.3, 127.2, 128.5, 128.6, 130.9, 132.5, 133.0, 136.5, 146.2; Anal. Calcd for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.07; H, 5.97; N, 19.02.

1-(4-Methylbenzyl)-*1H*-benzotriazole **4.1b.**

White prisms (92 %), mp 102.5-104.3 °C (methanol) (lit[56JCS1076] mp 106-107 °C): ^{1}H NMR δ 2.29 (s, 3 H), 5.77 (s, 2H), 7.09-7.18 (m, 4H), 7.28-7.37 (m, 3H), 8.03 (d, J = 8.0 Hz, 1H); ^{13}C NMR δ 21.0, 52.0, 109.7, 119.9, 123.7, 127.2, 127.5, 129.5, 131.7, 132.7, 138.2, 146.2.

1-(2-Chlorobenzyl)-1*H*-benzotriazole **4.1c.**

White prisms (98 %) mp 85-87 °C (acetonitrile) (lit[70AF1723] mp 87-88 °C): ^{1}H NMR δ 5.98 (s, 2H), 6.96 (dd, J = 7.7 and 1.6 Hz, 1H), 7.17 (td, J = 7.7 and 1.1 Hz, 1H), 7.21-7.29 (m, 1H), 7.34-7.45 (m, 4H), 8.07-8.10 (m, 1H); ^{13}C NMR δ 49.0, 109.5, 119.8, 123.8, 127.2, 127.4, 129.1, 129.6 (2C), 132.3, 132.8 (2C), 145.9.

1-(2-Chloro-6-fluorobenzyl)-1H-benzotriazole **4.1d.**

Colorless prisms (94 %) mp 107–108 °C (methanol): ^{1}H NMR δ 5.99 (d, J = 1.4 Hz, 2H), 7.08 (t, J = 9.0 Hz, 1H), 7.25–7.37 (m, 3H), 7.45 (t, J = 7.1 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 8.06 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 42.8 (d, J = 4.2 Hz), 109.2 (d, J = 2.6 Hz), 114.2 (d, J = 22.1 Hz), 119.4, 120.1 (d, J = 17.1 Hz), 123.5, 125.5 (d, J = 3.5 Hz), 127.1, 130.8 (d, J = 9.5 Hz), 132.4, 135.5 (d, J = 4.7 Hz), 145.4, 161.4 (d, J = 250.1 Hz); Anal. Calcd for $C_{13}H_9ClFN_3$: C, 59.67; H, 3.47; N, 16.06. Found: C, 59.46; H, 3.37; N, 16.08.

1-(4-Fluorobenzyl)-1*H*-benzotriazole **4.1e.**

Colorless prisms (78 %) mp 92.0–92.5 °C (methanol) (lit [92TL6405] mp not given): ^{1}H NMR δ 5.79 (s, 2H), 6.99 (t, J = 8.5 Hz, 2H), 7.23–7.40 (m, 5H), 8.04 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 51.2, 109.4, 115.8 (d, J = 21.6 Hz), 119.9, 123.8, 127.4, 129.2 (d, J = 8.4 Hz), 130.5 (d, J = 3.3 Hz), 132.5, 146.1, 162.4 (d, J =

246.1 Hz); Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.65; H, 4.32; N, 18.46.

1-(2-Fluorobenzyl)-1*H*-benzotriazole **4.1f**.

Brown prisms (87 %) mp 93.6-95.4 °C (methanol) (lit [93TL999] mp 93-95 °C): ^{1}H NMR δ 5.87 (s, 2H), 7.02–7.11 (m, 2H), 7.16–7.35 (m, 3H), 7.39–7.50 (m, 2H), 8.04 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 45.1 (d, J = 4.6 Hz), 109.4, 115.5 (d, J = 21.4 Hz), 119.8, 121.8 (d, J = 14.3 Hz), 123.8, 124.5, 127.4, 129.9 (d, J = 10.2 Hz), 130.3 (d, J = 32.4 Hz), 132.6, 146.0, 160.2 (d, J = 246.0 Hz); Anal. Calcd for $C_{13}H_{10}FN_3$: C, 68.71; H, 4.44; N, 18.49. Found: C, 68.78; H, 4.43; N, 18.59.

4.3.2 General Procedure for the Synthesis of Compounds **4.3a-f** and **4.5a-f**.

To a solution of **4.1** or **4.4** (4 mmol) in THF (50 mL) at –78 °C under argon was added *n*-BuLi (1.6*M*, 2.5 mL, 4 mmol). After 15 min. stirring, chloromethyltrimethylsilane **4.2** (0.49 g, 0.56 mL, 4 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight, before being washed with brine (2 × 20 mL) and dried ($MgSO_4$). The crude oil left after solvent removal under reduced pressure was subjected to flash chromatography with hexanes:ethyl ether = 3:1 to give the pure product.

1-[1-(2-Methylphenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3a**.

Colorless prisms (88 %) mp 109–110 °C (hexanes): ^{1}H NMR δ –0.13 (s, 9H), 1.71–1.78 (m, 1H), 2.15–2.23 (m, 1H), 2.40 (s, 3H), 6.26–6.31 (m, 1H), 7.14-7.34 (m, 6H), 7.51–7.54 (m, 1H), 8.02 (d, J =7.9 Hz, 1H); ^{13}C NMR δ –1.6, 19.4, 23.4, 57.6, 109.9, 119.9, 123.6, 126.4, 126.7, 126.9, 128.1, 130.9, 132.2, 135.0, 138.7, 146.3; Anal. Calcd for $C_{18}H_{23}N_3Si$: C, 69.86; H, 7.49; N, 13.58. Found: C, 69.96; H, 7.75; N, 13.70.

1-[1-(4-Methylphenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3b.**

Colorless prisms (90 %) mp 90-91 °C (hexanes): ^{1}H NMR δ –0.16 (s, 9H), 1.90–1.97 (m, 1H), 2.09–2.16 (m, 1H), 2.28 (s, 3H), 5.96 (t, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.26–7.43 (m, 5H), 8.02 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ –1.6 (3C), 21.0, 23.6, 61.1, 110.0, 120.0, 123.6, 126.7 (2C), 126.8, 129.4 (2C), 132.2, 137.9, 138.0, 146.4; Anal. Calcd for $C_{18}H_{23}N_3Si$: C, 69.86; H, 7.49; N, 13.58. Found: C, 70.04; H, 7.76; N, 13.69.

1-[1-(2-Chlorophenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3c.**

Yellow prisms (93 %) mp 94.1–95.1 °C (hexanes): ^{1}H NMR δ –0.12 (s, 9H), 1.80–1.87 (m, 1H), 2.20–2.28 (m, 1H), 6.45–6.50 (m, 1H), 7.16–7.20 (m, 2H), 7.31–7.51 (m, 5H), 8.04 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ –1.6 (3C), 24.5, 56.4, 109.6, 119.9, 123.9, 127.2, 127.7, 128.3, 129.2, 129.5, 131.7, 132.7, 139.2, 146.0; Anal. Calcd for $C_{17}H_{20}ClN_3Si$: C, 61.89; H, 6.11; N, 12.74. Found: C, 62.06; H, 6.22; N, 12.82.

1-[1-(2-Chloro-6-fluorophenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3d.**

White prisms (89 %) mp 66.7–67.7 °C (hexanes): ^{1}H NMR δ –0.04 (s, 9H), 2.32 (d, *J* = 6.6 Hz, 2H), 6.52 (t, *J* = 8.0 Hz, 1H), 6.93–6.99 (m, 1H), 7.18–7.47 (m, 5H), 8.04 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ –1.5, 20.8, 55.3, 109.8, 115.7 (d, *J* = 23.0 Hz), 120.0, 123.7, 126.1 (d, *J* = 2.6 Hz), 127.0, 130.3 (d, *J* = 10.0 Hz), 132.6, 133.9 (d, *J* =7.0 Hz), 146.2, 161.9 (d, *J* = 251.8 Hz); Anal. Calcd for $C_{17}H_{19}ClFN_3Si$: C, 58.69; H, 5.50; N, 12.08. Found: C, 59.09; H, 5.80; N, 12.16.

1-[1-(4-Fluorophenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4,3e.**

White prisms (96 %) mp 89.0–90.0 °C (hexanes): ^{1}H NMR δ –0.20 (s, 9H), 1.83–1.91 (m, 1H), 2.05–2.13 (m, 1H), 5.93 (t, *J* = 8.2 Hz, 1H), 6.94 (t, *J* = 8.5 Hz, 2H), 7.23–7.40 (m, 5H), 7.99 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR δ –1.7 (3C), 23.8, 60.5, 109.7, 115.7 (d, *J* = 21.4 Hz), 120.0, 123.8, 127.0, 128.5 (d, *J* = 8.0 Hz), 132.1, 136.8, 146.4, 161.9 (d, *J* = 246.2 Hz); Anal. Calcd for $C_{17}H_{20}FN_3Si$: C, 65.14; H, 6.43; N, 13.41. Found: C, 65.25; H, 6.64; N, 13.49.

1-[1-(2-Fluorophenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4,3f.**

Brown prisms (92 %) mp 85.6–86.4 °C (hexanes): ^{1}H NMR δ –0.13 (s, 9H), 1.94–2.01 (m, 1H), 2.15–2.22 (m, 1H), 6.33 (t, *J* = 8.2 Hz, 1H), 7.01–7.11(m, 2H), 7.20–7.26 (m, 1H), 7.33 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 8.7 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ –1.8 (3C), 23.6, 52.5, 109.5, 115.4 (d, *J* = 22.0 Hz), 119.8, 123.8, 124.8 (d, *J* = 3.5 Hz), 127.1, 128.3, 129.7 (d, *J* = 8.6 Hz), 132.5, 146.0, 159.2 (d, *J* = 244.4 Hz); Anal. Calcd for $C_{17}H_{20}FN_3Si$: C, 65.14; H, 6.43; N, 13.41. Found: C, 65.35; H, 6.55; N, 13.43.

1-[2-(1,1,1-Trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4,5a.**

Colorless oil (85 %): ^{1}H NMR δ 0.08 (s, 9H), 1.31–1.37 (m, 2H), 4.66–4.71 (m, 2H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.44–7.54 (m, 2H), 8.05 (d, *J* = 8.1 Hz, 1H); ^{13}C NMR δ –1.9 (3C), 18.1, 44.9, 109.3, 119.9, 123.6, 126.9, 132.3, 146.1; Anal. Calcd for $C_{11}H_{17}N_3Si$: C, 60.23; H, 7.81; N, 19.16. Found: C, 60.54; H, 8.19; N, 19.34.

1-[1-Methoxy-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4,5b.**

Colorless oil (72 %): ^{1}H NMR δ –0.07 (s, 9H), 1.43–1.50 (m, 1H), 1.66–1.74 (m, 1H), 3.14 (s, 3H), 6.02–6.07 (m, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 6.9 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ –

1.7(3C), 24.0, 56.0, 90.9, 111.2, 119.9, 124.0, 127.2, 130.8, 146.8; Anal. Calcd for $C_{12}H_{19}N_3OSi$: C, 57.79; H, 7.68; N, 16.85. Found: C, 58.15; H, 7.87; N, 17.13.

1-[1-Phenoxy-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.5c**.

Colorless oil (87 %): ^{1}H NMR δ 0.02 (s, 9H), 1.61–1.68 (m, 1H), 1.92–2.00 (m, 1H), 6.87–7.01 (m, 4H), 7.15 (t, *J* = 8.0 Hz, 2H), 7.31 (t, *J* =8.0 Hz, 1H), 7.44 (t, *J* = 7.1 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ –1.6 (3C), 24.6, 86.9, 111.2, 116.0 (2C), 120.0, 122.7 (2C), 124.1, 127.4, 129.6, 130.8, 146.7, 155.8; Anal. Calcd for $C_{17}H_{21}N_3OSi$: C, 65.56; H, 6.80; N, 13.49. Found: C, 65.90; H, 7.13; N, 13.42.

1-[1-(3-*N*,*N*-Diethylamino-phenoxy)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.5d**.

Colorless oil (93 %): ^{1}H NMR δ 0.06 (s, 9H), 1.04 (t, *J* = 7.1 Hz, 6H), 1.60–1.67 (m, 1H), 1.94–2.02 (m, 1H), 3.21 (q, *J* = 7.1 Hz, 4H), 6.18 (s, 1H), 6.26 (t, *J* = 10.1 Hz, 2H), 6.96–7.02 (m, 2H), 7.33 (t, *J* =8.0 Hz, 1H), 7.45 (t, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR δ –1.5 (3C), 12.4 (2C), 24.8, 44.3 (2C), 87.0, 99.5, 102.6, 106.2, 111.5, 120.0, 124.0, 127.3, 130.0, 130.9, 146.8, 149.0, 157.5; Anal. Calcd for $C_{21}H_{30}N_4OSi$: C, 65.93; H, 7.90; N, 14.64. Found: C, 65.56; H, 8.04; N, 14.74.

1-[1-Phenylthio-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.5e**.

Yellow prisms (74 %) (mp 64.5–65.5 °C): ^{1}H NMR δ –0.01 (s, 9H), 1.70–1.79 (m, 1H), 1.92–2.00 (m, 1H), 6.32–6.37 (m, 1H), 7.00–7.16 (m, 5H), 7.34 (t, *J* = 7.9 Hz, 1H), 7.45 (t, *J* = 7.4 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ –1.8 (3C), 23.7, 65.6, 111.3, 120.0, 123.8, 126.8, 128.6, 128.8 (2C), 131.2, 131.7, 133.3 (2C), 146.6; Anal. Calcd for $C_{17}H_{21}N_3SSi$: C, 62.34; H, 6.46; N, 12.83. Found: C, 62.44; H, 6.66; N, 12.79.

1-[1,2-Di(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.5f.**

White needles (89 %) (mp 101–102 °C): ^{1}H NMR δ –0.34 (s, 9H), 0.01 (s, 9H), 1.05 (dd, *J* = 13.3 and 2.6 Hz, 1H), 1.81–1.97 (m, 1H), 4.30 (dd, *J* = 13.3 and 2.6 Hz, 1H), 7.28-7.34 (m, 2H), 7.40–7.48 (m, 2H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ –3.4 (3C), –1.9 (3C), 17.4, 47.8, 109.6, 119.9, 123.4, 126.5, 133.2, 145.5; Anal. Calcd for $C_{14}H_{25}N_3Si_2$: C, 57.68; H, 8.64; N, 14.41. Found: C, 57.96; H, 8.80; N, 14.38.

4.3.3 Preparation of 1-{1-(4-Methylphenyl)-1-[(1,1,1-trimethylsilyl)methyl]nonyl}-1*H*-1,2,3-benzotriazole **4.6.**

To a solution of **4.3b** (0.618g, 2 mmol) in THF (50 mL) at –78 °C was added *n*-BuLi in hexanes (1.6*M*, 1.3 mL, 2 mmol). After 20 min. 1-iodooctane (0.492, 2 mmol, 0.37 mL) was added. The mixture was stirred at –78 °C for an additional 4 h and allowed to warm to room temperature overnight. The reaction mixture was washed with saturated aqueous ammonium chloride solution (2 × 20 mL), extracted with diethyl ether (2 × 20 mL), washed with brine (2 × 20 mL), and dried ($MgSO_4$). After the solvent was removed, the residue was subjected to flash chromatography with hexanes:diethyl ether = 3:1 to give the pure product as yellowish prisms (0.830 g, 98%) mp 90.2–91.7 °C: ^{1}H NMR δ –0.28 (s, 9H), 0.72–0.85 (m, 4H), 1.14–1.20 (m, 12H), 2.03–2.12 (m, 1H), 2.32–2.40 (m, 4H), 2.51–2.75 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 7.03–7.12 (m, 5H), 7.21 (t, *J* = 7.5 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR δ –0.6 (3C), 14.0, 20.9, 22.5, 23.5, 27.9, 29.0, 29.2, 29.5, 31.7, 39.2, 70.2, 112.4, 119.7, 123.2, 126.0 (3C), 129.1 (2C), 132.2, 137.3, 141.5, 147.0; Anal. Calcd for $C_{26}H_{39}N_3Si$: C, 74.05; H, 9.32; N, 9.96. Found: C, 74.36; H, 9.55; N, 10.10.

4.3.4 Preparation of 2-(4-Methylphenyl)-1-decene **4.7.**

1-{1-(4-Methylphenyl)-1-[(1,1,1-trimethylsilyl)methyl]nonyl)-1*H*-1,2,3-benzotriazole **4.6** (0.422 g, 1 mmol) was distilled on the Kugelrohr apparatus under reduced pressure (1 mm Hg) at 110 °C over 2 hours . The distillate was washed with sodium hydroxide solution (5%, 2 × 20 mL), saturated aqueous ammonium chloride solution (2 × 20 mL), brine (2 × 20 mL) and dried ($MgSO_4$). After the solvent was removed under reduced pressure, the remaining oil was pure product (colorless oil, 0.205 g, 89 %): ^{1}H NMR δ 0.99–1.03 (m, 3H), 1.39–1.58 (m, 12H), 2.46 (s, 3H), 2.61 (t, *J* = 6.9 Hz, 2H), 5.13 (d, *J* = 0.6 Hz, 1H), 5.36 (d, *J* = 1.2 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 2H), 7.43 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR δ 14.1, 21.0, 22.7, 28.3, 29.3, 29.4, 29.5, 31.9, 35.4, 111.2, 126.0 (2C), 128.9 (2C), 136.8, 138.5, 148.5; Anal. Calcd for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 88.38; H, 11.77.

4.3.5 Preparation of 1-Chloro-3-fluoro-2-vinylbenzene **4.8.**

Method A: Compound **4.3d** (0.348 g, 1 mmol) was dissolved in TBAF in THF (1*M*, 1.2 mL, 1.2 mmol). The mixture was stirred under reflux for 6 hours, cooled, and water (30 mL) and dichloromethane (40 mL) added. The resulting emulsion was filtered through Celite, the aqueous layer extracted with dichloromethane (2 × 20 mL), organic layer dried ($MgSO_4$) and solvent removed under reduced pressure. The remaining oil was subjected to column chromatography on silica gel with hexanes:diethyl ether = 5:1 to give the product (colorless oil, 0.120 g, 77 %).

Method B: Cesium fluoride (0.228 g, 1.5 mmol), **4.3d** (0.348 g, 1 mmol) and 18-crown-6 (0.15 mmol, 0.0039 g) were dissolved in DMF (4 mL) under Ar and stirred at 100 °C for 5 days. The cold reaction mixture was treated with water (50 mL) and extracted with hexanes (5 × 20 mL), the organic layer washed with water (3 × 30 mL) and dried ($MgSO_4$). After the solvent was removed under reduced pressure, the remaining oil was pure product (colorless oil, 0.127 g, 81 %): ^{1}H NMR δ 5.64 (d, *J* =

11.7 Hz, 1H), 6.96 (d, J = 18.0 Hz, 1H), 5.54 (dd, J = 18.0 and 11.7 Hz, 1H), 6.97 (t, J = 9.9 Hz, 1H), 7.06–7.18 (m, 2H); ^{13}C NMR δ 114.6 (d, J = 23.4 Hz), 122.2 (d, J = 11.5 Hz), 124.4, 125.4, 127.5, 128.3 (d, J = 10.0 Hz), 134.4 (d, J = 5.6 Hz), 161.3 (d, J = 251.0 Hz); Anal. Calcd for C_8H_6ClF: C, 61.36; H, 3.86. Found: C, 61.02; H, 3.76.

4.3.6 General Procedure for the Synthesis of Compounds **4.10a-d.**

The corresponding benzotriazole derivative **4.3** or **4.5** (2 mmol) was dissolved in THF (50 mL), cooled to –78 °C and *n*-BuLi in hexanes, added (1.6 *M*, 1.25 mL, 2 mmol). After 15 min. stirring, the corresponding aldehyde (2 mmol) was added and the mixture was allowed to warm-up to room temperature over 16 hours. The reaction mixture was washed with brine (2 × 20 mL) and dried. After solvent removal the remaining oil was subjected to flash column chromatography with hexanes:diethyl ether = 5:1 to give the pure product.

{[1-(3-Methoxyphenyl)-2-(4-methylphenyl)-allyl]oxy}-(trimethyl)silane **4.10a**.

Colorless oil (72 % yield): ^{1}H NMR δ 0.11 (s, 9H), 2.27 (s, 3H), 3.74 (s, 3H), 5.40 (s, 1H), 5.44 (s, 1H), 5.57 (s, 1H), 6.72 (dd, J = 8.4 and 1.8 Hz, 1H), 6.89–6.91 (m, 2H), 7.02 (d, J = 8.0 Hz, 2H), 7.13–7.20 (m, 3H); ^{13}C NMR δ 0.1 (3C), 21.0, 55.0, 76.7, 112.5 (2C), 113.5, 119.3, 127.1 (2C), 128.6 (2C), 128.9, 136.7, 136.9, 144.5, 150.5, 159.5; Anal. Calcd for $C_{20}H_{26}O_2Si$: C, 73.57; H, 8.03. Found: C, 73.97; H, 8.31.

{[1-*t*-Butyl-2-(4-methylphenyl)-allyl]oxy}-(trimethyl)silane **4.10b**.

Colorless oil (87 % yield): ^{1}H NMR δ 0.15 (s, 9H), 0.73 (s, 9H), 2.33 (s, 3H), 4.34 (s, 1H), 5.28 (s, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H); ^{13}C NMR δ 0.3 (3C), 21.1, 26.7 (3C), 36.5, 81.3, 115.9, 126.7 (2C), 128.9 (2C),

136.7, 140.3, 150.5; Anal. Calcd for $C_{17}H_{28}OSi$: C, 73.85; H, 10.21. Found: C, 74.08; H, 10.42.

{[2-(4-Fluorophenyl)-1-(3-methoxyphenyl)allyl]oxy}(trimethyl)silane **4.10c**.

Colorless oil (52 % yield): ^{1}H NMR δ 0.11 (s, 9H), 3.71 (s, 3H), 5.35 (s, 1H), 5.44 (s, 1H), 5.54 (s, 1H), 6.71–6.73 (m, 1H), 6.84–6.90 (m, 4H), 7.14 (t, J = 8.3 Hz, 1H), 7.21–7.26 (m, 2H);^{13}C NMR δ 0.0 (3C), 55.0, 77.0, 112.4 (d, J = 5.9 Hz), 114.3, 114.5, 114.8, 119.1 (2C), 129.0 (d, J = 7.1 Hz, 2C), 135.5, 144.1, 149.8, 159.5, 162.1 (d, J = 244.6 Hz); Anal. Calcd for $C_{19}H_{23}FO_2Si$: C, 69.06; H, 7.01. Found: C, 69.17; H, 7.34.

{[2-[1-(1,2,3-benzotriazol-1-yl)]-1-(3-methoxyphenyl)allyl]oxy}(trimethyl) silane **4.10d**.

Colorless oil (70 % yield): ^{1}H NMR δ 0.08 (s, 9H), 5.53 (s, 1H), 5.60 (s, 1H), 6.16 (s, 1H), 7.13–7.20 (m, 3H), 7.29–7.34 (m, 3H), 7.38–7.48 (m, 2H), 8.00 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ – 0.1 (3C), 74.2, 107.8, 110.5, 119.8, 124.0, 126.7 (2C), 127.8, 127.9, 128.1 (2C), 132.9, 140.4, 145.7, 146.4; Anal. Calcd for $C_{18}H_{21}N_3OSi$: C, 66.84; H, 6.89; N, 12.99. Found: C, 66.51; H, 6.89; N, 13.06.

4.3.7 Preparation of 1-(3-Methoxyphenyl)-2-(2-methylphenyl)-2-propen-1-ol **4.11**.

1-[1-(2-Methylphenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3a** (0.619g, 2 mmol) was dissolved in THF (50 mL), cooled to –78 °C, and *n*-BuLi in hexanes, added (1.6 *M*, 1.25 mL, 2 mmol). After 15 min. stirring, 3-methoxybenzaldehyde (0.27 g, 2 mmol, 0.24 mL) was added, the mixture allowed to warm to rt. over 16 h, and stirred under reflux for 3 h. The reaction mixture was washed with brine (2 × 20 mL) and dried. After solvent removal the remaining oil was dissolved in TBAF in THF (1 *M*, 2.4 mL, 2.4 mmol) and stirred at room temperature for 2 h. After solvent removal, the remaining oil was subjected to flash column

chromatography with hexanes:diethyl ether = 1:1 to give the pure product (colorless oil, 0.356 g, 70 %): ^{1}H NMR δ 2.07 (s, 3H), 2.58 (br s, 1H), 3.65 (s, 3H), 5.01 (s, 1H), 5.30 (s, 1H), 5.56 (s, 1H), 6.73–6.79 (m, 3H), 6.86 (d, J = 7.2 Hz, 1H), 6.99–7.15 (m, 4H); ^{13}C NMR δ 19.5, 55.0, 77.2, 112.0, 113.4, 113.9, 119.1, 125.0, 127.1, 129.0, 129.1, 129.9, 135.8, 139.5, 143.2, 150.9, 159.3; Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.09; H, 7.48.

4.3.8 Preparation of *N*1-Phenyl-2-(4-methylphenyl)-acrylamide **4.11** and *N*1-phenyl-2-(1*H*-1,2,3-benzotriazol-1-yl)-2-(4-methylphenyl)-3-(1,1,1-trimethylsilyl)propanamide **4.12**.

1-[1-(4-Methylphenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3b** ((0.619 g, 2 mmol) was dissolved in THF (50 mL), cooled to –78 °C and *n*-BuLi in hexanes added (1.6 *M*, 1.25 mL, 2 mmol). After 15 min. stirring, phenyl isocyanate (0.24 g, 2 mmol, 0.23 mL) was added and the mixture was allowed to warm-up to room temperature over 16 hours. (a) The solvent was removed under a stream of argon and the remaining oil was heated at 130 °C for 1h. Methylene chloride (30 mL) and water (20 mL) were added to the cold reaction mixture. The organic layer was washed with brine (2 × 20 mL) and dried ($MgSO_4$). After solvent removal the remaining oil was subjected to flash chromatography with hexanes:diethyl ether = 1:1 to give pure **4.11** (colorless plates, 0.305 g, 64 %) mp 136.6–137.4 °C : ^{1}H NMR δ 2.38 (s, 3H), 5.67 (s, 1H), 6.20 (s, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.20–7.33 (m, 7H), 7.51 (d, J =7.5 Hz, 2H); ^{13}C NMR δ 21.2, 119.8 (2C), 122.4, 124.4, 128.0 (2C), 128.9 (2C), 129.5 (2C), 133.6, 137.7, 138.7, 144.9, 165.4; Anal. Calcd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.85; H, 6.64; N, 5.93. (b) The reaction mixture was washed with brine (2 × 20 mL) and dried. After solvent removal the remaining oil was subjected to flash chromatography with hexanes:diethyl ether = 1:1 to give pure **4.12** (colorless prisms, 0.571 g, 92 %) mp 130–132 °C: ^{1}H NMR δ –0.20 (s, 9H), 2.28 (d, J = 14.6 Hz, 1H), 2.34 (s, 3H), 2.57 (d, J = 14.6 Hz, 1H),

6.82 (d, J = 8.2 Hz, 1H), 7.11–7.15 (m, 3H), 7.23–7.35 (m, 6H), 7.46 (d, J = 8.3 Hz, 2H), 8.06 (d, J = 8.3 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR δ –0.6 (3C), 21.0, 29.1, 75.0, 112.7, 120.1, 120.6 (2C), 124.3, 124.9, 126.6 (2C), 127.6, 128.9 (2C), 129.5 (2C), 133.1, 137.3, 137.9, 138.5, 146.4, 167.8; Anal. Calcd for $C_{25}H_{28}N_4OSi$: C, 70.06; H, 6.58; N, 13.07. Found: C, 70.32; H, 6.87; N, 13.07.

4.3.9 Preparation of *N*1-Phenyl-2-(1*H*-1,2,3-benzotriazol-1-yl)-2-(4-methylphenyl) propanamide **4.13.**

Compound **4.12** (0.428 g, 1 mmol) and TBAF in THF (1 *M*, 1.2 mL, 1.2 mmol) were stirred under reflux for 2 hours. Water (30 mL) was added to the reaction mixture, extracted with methylene chloride (30 mL) and filtered through Celite. The organic layer was washed with water (2 × 20 mL) and dried ($MgSO_4$). After solvent removal, the remaining oil was recrystallized from methanol (white prisms, 0.259 g, 73 %) mp 199.0–200.1 °C: ^{1}H NMR δ 2.38 (s, 3H), 2.57 (s, 3H), 6.87 (d, J = 7.7 Hz, 1H), 7.10–7.22 (m, 5H), 7.26–7.43 (m, 6H), 7.82 (br s, 1H), 8.09 (d, J = 7.4 Hz, 1H); ^{13}C NMR δ 21.2, 27.2, 72.6, 112.3, 120.3, 120.5 (2C), 124.3, 125.2, 126.7 (2C), 127.9, 129.1 (2C), 129.9 (2C), 133.3, 136.5, 137.0, 139.0, 146.5, 167.8; Anal. Calcd for $C_{22}H_{20}N_4O$: C, 74.14; H, 5.66; N, 15.72. Found: C, ; H, ; N,

4.3.10 Preparation of 3-(1*H*-1,2,3-Benzotriazol-1-yl)-3-(2-chlorophenyl)-1-phenyl-4-(1,1,1-trimethylsilyl)-1-butanol **4.15.**

1-[1-(2-Chlorophenyl)-2-(1,1,1-trimethylsilyl)ethyl]-1*H*-1,2,3-benzotriazole **4.3c** (0.659 g, 2 mmol) was dissolved in THF (50 mL) and cooled to –78 °C. *n*-BuLi in hexanes (1.6 *M*, 1.25 mL, 2 mmol) was added and the green solution was stirred for additional 15 min. Styrene oxide (0.24 g, 2 mmol, 0.25 mL) was added and the mixture allowed to warm to room temperature overnight. The yellow reaction mixture was washed with saturated aqueous ammonium chloride solution (70 mL), the aqueous layer extracted with ethyl ether (2 × 30 mL) and the combined organic layer

washed with brine (2 × 20 mL) and dried ($MgSO_4$). After solvent removal, the remaining oil was subjected to flash column chromatography on silica gel with hexanes:diethyl ether = 1:1 to give the product (white prisms, 0.648g, 72 %) mp 156.2–158.6 °C: ^{1}H NMR δ –0.18 (s, 9H), 2.81–2.97 (m, 3H), 3.25–3.32 (m, 1H), 4.18 (br s, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.83 (br s, 1H), 7.04–7.39 (m, 8H), 7.67 (d, *J* = 7.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR δ –0.5 (3C), 24.7, 47.5, 69.4, 70.2, 110.9, 119.9, 123.4, 125.1, 126.3, 126.9, 127.2, 127.6, 128.2 (4C), 129.5, 131.9, 132.6, 134.2, 139.7, 145.1, 146.8; Anal. Calcd for $C_{25}H_{28}ClN_3OSi$: C, 66.72; H, 6.27; N, 9.34. Found: C, 66.76; H, 6.35; N, 9.35.

4.3.11 Preparation of 3-(2-Chlorophenyl)-1-phenyl-3-buten-1-ol **4.16**.

Compound **4.15** (0.450 g, 1 mmol) was dissolved in TBAF in THF (1 *M*, 1.2 mL, 1.2 mol). *n*-BuLi in hexanes (1 *M*, 0.65 mL, 1 mmol) was added with cooling at 0 °C. The mixture was stirred at rt. for 40 hours. Water (30 mL) and dichloromethane (40 mL) was added and the resulting emulsion filtered through Celite, the aqueous layer extracted with dichloromethane (2 × 20 mL), organic layer dried ($MgSO_4$) and solvent removed under reduced pressure. The remaining oil was subjected to flash column chromatography with hexanes:diethyl ether = 1:1 to give the product (yellow oil, 0.210 g, 81 %): ^{1}H NMR δ 2.28 (d, *J* = 2.0 Hz, 1H), 2.78 (dd, *J* =14.6 and 9.6 Hz, 1H), 2.96 (dd, *J* = 14.3 and 3.6 Hz, 1H), 4.56 (dt, *J* = 9.0 and 3.1 Hz, 1H), 5.14 (s, 1H), 5.36 (s, 1H), 7.18–7.28 (m, 8H), 7.34–7.37 (m, 1H); ^{13}C NMR δ 47.0, 71.7, 119.1, 125.8 (2C), 126.6, 127.4, 128.2 (2C), 128.5, 129.6, 130.4, 132.0, 140.8, 143.7, 144.8; Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.27; H, 5.84. Found: C, 74.44; H, 6.23.

4.3.12 Preparation of 3-[1-(1-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methylphenyl)-2-(1,1,1-trimethylsilyl)-ethyl]-1-cyclohexanone **4.17.**

Compound **4.3b** (0.618 g, 2 mmol) was dissolved in THF (50 mL), cooled to -78 °C, and *n*-BuLi in hexanes added (1.6 *M*, 1.25 mL, 2 mmol). After 15 min. stirring, cyclohexen-3-one (0.190 g, 2 mmol, 0.194 mL) was added and the mixture allowed to warm-up to room temperature over 16 hours. The reaction mixture was washed with brine (2 × 20 mL) and dried. After solvent removal the remaining solid was subjected to flash column chromatography with hexanes:diethyl ether = 1:1 to give the product (white prisms, 0.673 g, 83%) mp 180.9–182.8 °C: ^{1}H NMR δ –0.22 (s, 9H), 1.15 (q, *J* = 12.9 Hz, 1H), 1.97 (t, *J* = 13.5 Hz, 2H), 2.12–2.24 (m, 4H), 2.39–2.53 (m, 3H), 2.70 (d, *J* = 13.1 Hz, 1H), 2.90 (d, *J* = 13.5 Hz, 1H), 3.68 (t, *J* = 13.3 Hz, 1H), 6.57 (d, *J* = 8.5 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 2H), 7.24–7.32 (m, 4H), 7.40 (t, *J* = 7.4 Hz, 1H), 8.18 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ –0.9 (3C), 20.8, 24.3, 27.3, 28.5, 40.9, 44.1, 44.5, 73.2, 113.3, 119.7, 123.3, 126.1, 127.6 (2C), 128.7 (2C), 133.0, 136.5, 137.7, 146.5, 210.2; Anal. Calcd for $C_{24}H_{31}N_3OSi$: H, 7.70; N, 10.36. Found: H, 7.80; N 9.98.

4.3.14 Preparation of 3-[1-(4-Methylphenyl)vinyl]-1-cyclohexanone **4.28.**

Compound **4.17** (0.405 g, 1 mmol) was dissolved in TBAF in THF (1 *M*, 1.5 mL, 1.5 mmol) under Ar and stirred under reflux for 4 hours. The reaction mixture was dissolved in methylene chloride (30 mL) and washed with sodium hydroxide solution (5%, 2 × 20 mL), hydrochloric acid (3%, 2 × 20 mL), brine (2 × 20 mL) and dried ($MgSO_4$). After solvent removal the remaining oil was subjected to column chromatography with hexanes:diethyl ether = 3:1 to give the product (colorless oil, 0.159 g, 74 %): ^{1}H NMR δ 1.51–1.70 (m, 2H), 1.94–2.06 (m, 2H), 2.23–2.40 (m, 6H), 2.50–2.56 (m, 1H), 2.92–2.99 (m, 1H), 5.01 (s, 1H), 5.21 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR δ 20.9, 24.7, 30.4, 41.2, 42.6,

46.9, 111.3, 126.3 (2C), 128.9 (2C), 137.1, 138.5, 151.7, 211.0; Anal. Calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 83.94; H, 8.56.

4.3.15 Preparation of 2-(1*H*-1,2,3-Benzotriazol-1-yl)-1-(4-methoxyphenyl)-2-(4-methylphenyl)-3-(1,1,1-trimethylsilyl)-1-propanone **4.19.**

Compound **4.3b** (1.238 g, 4 mmol) was dissolved in THF (50 mL) and cooled to –78 °C, and *n*-BuLi in hexanes added (1.6 *M*, 2.63 mL, 4 mmol). After 15 min. stirring, *p*-anisoyl chloride (0.720 g, 4 mmol, 0.52 mL) was added and the mixture allowed to warm-up to room temperature over 16 hours. The reaction mixture was washed with ammonium saturated aqueous chloride solution (2 × 20 mL), extracted with ethyl ether (2 × 20 mL), washed with brine (2 × 20 mL) and dried ($MgSO_4$). After solvent removal the remaining oil was subjected to flash column chromatography with hexanes:diethyl ether = 3:1 to give the product (oil that turns into a colorless glass when put under high vacuum, 1.650 g, 93 %): ^{1}H NMR δ –0.20 (s, 9H), 2.36 (d, *J* = 14.8 Hz, 4H), 2.54 (d, *J* = 14.8 Hz, 1H), 3.74 (s, 3H), 6.68 (d, *J* = 9.0 Hz, 2H), 6.98–7.01 (m, 1H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.19–7.25 (m, 4H), 7.55 (d, *J* = 9.0 Hz, 2H), 7.99–8.02 (m, 1H); ^{13}C NMR δ 0.2 (3C), 21.0, 31.0, 55.3, 77.5, 112.5, 113.4 (2C), 119.9, 123.7, 127.0, 128.0, 128.1 (2C), 128.9 (2C), 132.1 (2C), 133.5, 136.5, 138.2, 146.7, 163.0, 194.5; Anal. Calcd for $C_{26}H_{29}N_3OSi$: C, 70.39; H, 6.59; N 9.47. Found: C, 70.02; H, 6.65; N 9.43.

4.3.16 Preparation of 1-(4-Methoxyphenyl)-2-(4-methylphenyl)-2-propen-1-one **4.20** and (*E*)-1-(4-Methoxyphenyl)-3-(4-methylphenyl)-2-propen-1-one **4.21.**

Compound **4.19** (0.444 g, 1 mmol), cesium fluoride (0.228 g, 1.5 mmol) and 18-crown-6 (0.0039 g, 0.15 mmol) was dissolved in DMF (4 mL) and stirred at 100 °C for 40 min. To the cold reaction mixture was added water (100 mL) and dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL), the combined organic layer washed with water (5 × 50 mL) and dried

($MgSO_4$). After solvent removal the remaining yellow semi-solid was subjected to column chromatography with hexanes:diethyl ether = 3:1 to give **4.20** as the first fraction (R_f = 0.47) (colorless oil, 0.181 g, 72 %): ^{1}H NMR δ 2.31 (s, 3H), 3.80 (s, 3H), 5.48 (s, 1H), 5.93 (s, 1H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.90 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 21.0, 55.3, 113.5 (2C), 117.6, 126.5 (2C), 129.2 (2C), 129.8, 132.2 (2C), 134.2, 138.1, 148.3, 163.6, 196.3; HRMS Calcd for $C_{17}H_{16}O_2$ 252.1150, found 252.1135. The second fraction (R_f = 0.30) was **4.21** (white needles, 0.055 g, 22 %) mp 125.8–126.7 °C (lit [93TL999] mp 126 °C): ^{1}H NMR δ 2.39 (s, 3H), 3.89 (s, 3H), 6.98 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.51 (d, *J* = 15.5, 1H), 7.54 (d, *J* = 8.0 Hz, 2H), 7.79 (d, *J* = 15.5 Hz, 1H), 8.03 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR δ 21.4, 55.4, 113.8 (2C), 120.9, 128.3 (2C), 129.6 (2C), 130.7 (2C), 131.2, 132.3, 140.7, 143.9, 163.3, 188.7.

CHAPTER 5
VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN WITH BENZOTRIAZOLE BEARING ANIONS

5.1 Introduction

Nucleophilic substitution of hydrogen in nitroarenes, although known for a long time, has received increased attention during the last two decades [78TL3495]. Figure 5.1 presents the mechanism for nucleophilic substitution of aromatic nitro compounds.

In all cases the rate of addition of nucleophiles to a hydrogen-substituted site of an aromatic nitro compound (k_2) is faster than the addition to an X-substituted site (k_1). This is due to the absence of electrostatic repulsion between the hydrogen atom and the incoming nucleophile and the lower steric requirements at an H-substituted versus a X-substituted position [84MI1, 82CR77]. Usually, the substitution of hydrogen is not observed due to the reluctance of hydride to act as a leaving group.

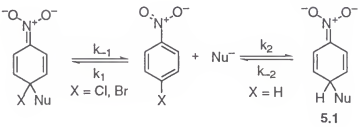


Figure 5.1

The σ^Hcomplex **5.1** though will give the H substitution product if is treated with an oxidant or bromine, followed by a base [78HCA449]. The most important method remains the one in which the elimination of the hydrogen is promoted by the concomitant departure of a part of the nucleophilic addend [83MI1] called vicarious nucleophilic substitution (VNS), wich has been extensively reviewed [91S103, 92PJC3, 87ACR282].

Previous work in the Katritzky group has shown that benzotriazole is as good a leaving group as a halogen in some reactions[91T2683, 94AA31, 94CSR363, 94S445]. This feature has been used successfully in our group for the synthesis of aromatic nitroaldehydes [96TL347]. There has been only one previous report of using benzotriazole in vicarious nucleophilic substitution i.e. with 1-(phenylsulfonylmethyl)benzotriazole, in which case the sulfonyl was the leaving group [95TL2169].

This chapter demonstrates the use of benzotriazole adducts for the syntheses of nitroaryldiarylmethanes (*via* VNS) and of aromatic nitroketones (*via* oxidative nucleophilic substitution of hydrogen ONSH).

5.2 First General Synthesis of *p*-(Nitroaryl)diarylmethanes *via* Vicarious Nucleophilic Substitution of Hydrogen

Substituted triarylmethanes are of considerable interest as leuco dyes [94DP303], photochromic agents [90MI1] and as substrates for theoretical studies [92JOC3924]. While many methods are available for the preparation of symmetrical triarylmethanes [73TL679, 74JCS(P1)2077, 89JHC1563, 49JA2209, 58JA4388], syntheses of unsymmetrical triarylmethanes are less developed. General methods include (i) condensation of unsymmetrical benzhydrols with phenols under acidic [81S125] or basic conditions [58ZOB586], or with *N,N*-dimethylaniline or alkoxybenzenes under acidic conditions [53JA275, 94H345] and (ii) displacement of benzotriazole in (benzotriazol-1-yl)diphenylmethanes either by electron rich arene catalyzed by $ZnCl_2$ [94H345] or by 4-(*N,N*-dimethyamino)phenylmagnesium bromide [94DP303]. Unsymmetrical di(aryl)methyl -indoles, pyrroles and pyridines were synthesized by condensation of the corresponding heterocycle with diarylmethanols [94DP303] or by Lewis acid catalyzed displacement of benzotriazole in (benzotriazol-1-yl)diphenylmethanes [94H345]. However, to the best of our knowledge, unsymmetrical nitro-substituted triarylmethanes have not been previously synthesized: such compounds could be of significant versatility due to the

easy reduction of the nitro group, and subsequent transformations of the resulting amino derivatives.

Vicarious nucleophilic substitution of hydrogen (VNS) using carbon nucleophiles, developed by Makosza *et al.* [87ACR282, 91S103], has become a useful tool for introducing C-linked substituents into electrophilic arenes. While VNS has been used for syntheses of (nitro-aryl)arylmethanes [82AG(E)451, 84JOC1494], no such syntheses of (nitroaryl)diarylmethanes have appeared.

Reactions of tris(benzotriazol-1-yl)methane with nitroarenes [96TL347] in this laboratory showed that benzotriazole derivatives readily undergo VNS with benzotriazolate anion acting as a leaving group. We now demonstrate that nitroarenes undergo VNS when treated with benzotriazolyldiarylmethanes in THF in the presence of potassium *tert*-butoxide, that condensations of benzotriazole with diarylmethanols in the presence of catalytic amounts of *p*-toluenesulfonic acid [90JCS(P2)2059] is a useful *umpolung* in building triarylmethanes, and that oxidative nucleophilic substitution of hydrogen in nitroarenes [96JCS(CC)837, 94T4913] is a common side-process in benzotriazole mediated VNS chemistry.

5.3 Results and Discussion

A series of diarylmethanols **5.2** were used as substrates for this study (Table 5.1). While compounds **5.2a-f** were commercially available materials, compounds **5.2g-k** were synthesized by published or new procedures. Compound **5.2g** was obtained in 98% yield by reduction of the corresponding benzophenone with sodium borohydride. Compound **5.2h** was obtained by the reaction of 4-methylphenylmagnesium bromide with *o*-anisaldehyde in 88% yield Compounds **5.2i** and **5.2j** were synthesized by the reaction of the corresponding aldehyde with 4-(*N,N*-dimethylamino)phenylmagnesium bromide in 56 and 73% yield, respectively by means of our previously reported procedure [94DP303].

In an effort to test a heterocyclic substrate, compound **5.2k** was synthesized by α-lithiation of 2-methylthiophene [77JCS(P1)887] and subsequent reaction with *p*-anisaldehyde in 47% yield. New compounds **5.2h-k** were fully characterized.

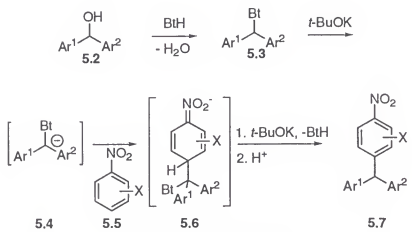
Table 5.1 Diarylmethanols for the Synthesis of *p*-(Nitroaryl)diarylmethanes

5.2

5.2	Ar^1	Ar^2	Yield %
a	phenyl	phenyl	-
b	phenyl	2-methylphenyl	-
c	phenyl	4-chlorophenyl	-
d	phenyl	4-biphenyl	-
e	phenyl	4-methoxyphenyl	-
f	4-methylphenyl	phenyl	-
g	4-(*N,N*-dimethylamino)phenyl	phenyl	98
h	4-methylphenyl	2-methoxyphenyl	88
i	4-(*N,N*-dimethylamino)phenyl	4-*n*-hexyloxyphenyl	56
j	4-(*N,N*-dimethylamino)phenyl	3,4,5-trimethoxyphenyl	73
k	4-methoxyphenyl	5-methylthien-2-yl	47

(Diarylmethyl)benzotriazoles of type **5.3** (Figure 5.2) were previously prepared in this group from benzotriazole and diarylmethanols in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*TSA) in benzene with azeotropic removal of water[90JCS(P2)2059]. We now find that the use of perfluorocarbon fluids for water removal[93S953] (for additional uses of these reagents in benzotriazole chemistry see Chapter 6), diarylmethanols, benzotriazole in 1.3 molar excess and a catalytic amount of *p*TSA (or even without catalyst in case of **5.2e,g–k**), give the 1- and 2-(diarylmethyl)benzotriazoles **5.3a-k** mixtures in almost quantitative yields with respect to the diarylmethanols **5.2a-k** (Figure 5.2). These mixtures were used directly after removal of excess benzotriazole.

The (diarylmethyl)benzotriazoles **5.3** were reacted with a series of *o*- and *m*-substituted nitrobenzenes **5.5**. An equimolar mixture of **5.3** and **5.5** was added to a solution of potassium *t*-butoxide in dry THF to give a deep red reaction mixture. Upon quenching with saturated ammonium chloride solution, (nitroaryl)diarylmethanes **5.7** were obtained (Figure 5.2 and Table 5.2). Reaction times were limited to 4 hours since longer reaction times lowered the observed yields of the desired product **5.6**. Temperature needed



Note: for designation of Ar^1, Ar^2 and X see Table 5.2

Figure 5.2

to be carefully controlled: study showed that carbanions of types **5.3** generated from the corresponding 1-(diarylmethyl)benzotriazoles **5.2** with *ca.* 5 equiv. of potassium *tert*-butoxide in dry THF are stable at –20 °C. However, higher temperatures cause triazole ring fragmentation as evidenced by detection of benzophenones in the GCMS spectra of the reaction mixture, probably through a pathway previously described [91CB1431].

The addition step of anions **5.4** to nitroarenes **5.5** to form σ^H-adducts of type **5.6** (Figure 5.2) is fast, as evidenced by a reaction between 3-nitroanisole and **5.2c** that was quenched at –20 °C after 10 min with a non-degassed aqueous acidic solution to give compound **5.8r** as the only product observed (Figure 5.3). Compounds of type **5.8** are products of oxidative nucleophilic substitution (ONSH) [96JCS(CC)837] and their

formation indicates a high concentration of adduct **5.6** in the early stages of the reaction[92PJC3]. The elimination of the benzotriazole from adducts of type **5.6** (Figure 5.2) works well for unsubstituted, *o*-chloro-, *o*-fluoro- and *o*-phenyl-substituted nitrobenzenes **5.5** to give **5.6a–e, m** in good to excellent yields regardless of the structure of compound **5.2** (Table 5.2) but is slow with *o*-bromonitrobenzene (**5.5**, X =2-Br) (affording **5.7f** and **5.6g** in only 52 and 38% yield respectively) and does not work

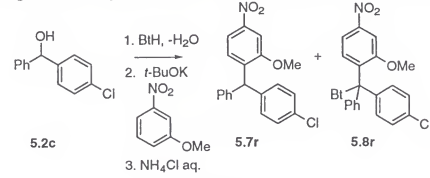


Figure 5.3

at all for *o*-iodonitrobenzene (**5.5**, X = 2-I). The reactions of *o*-methoxynitrobenzene (**5.5**, X = 2-MeO) show how the structure of the diarylmethanol **5.2** influences the outcome of the reaction: the electron rich **5.2i** and **5.2k**, and the sterically hindered **5.2b** gave low yields of the VNS product. A comparison between the reaction of **5.2a** with unsubstituted nitrobenzene (**5.5**, X = H) and *o*-methoxynitrobenzene (**5.5**, X = MeO) suggests that the more electron rich adduct **5.6h** eliminates benzotriazole more slowly than **5.6a**. *o*-*t*-Butylnitrobenzene (**5.5**, X = 2-*tert*-Bu) and *o*-trifluoromethylnitrobenzene (**5.5**, X = 2-CF_3) underwent VNS to give only 33% and 50% yields respectively, of the corresponding nitroaryldiarylmethanes. *m*-Substituted nitrobenzenes **5.5** show the same slow elimination rate to give the VNS products: *m*-fluoro and *m*-methoxynitrobenzenes **5.5** gave the VNS products in moderate yields. In case of the latter, compound **5.8r** was isolated and fully characterized in 8% yield. Surprisingly, 1-nitronaphthalene reacts cleanly and gives the VNS product in 94% yield. Most likely the bimolecular [87ACR282] elimination step **5.6**→**5.7** which needs elevated temperatures and high base concentration

to achieve a reasonable rate, is rate controlling. Process **5.6**→ **5.7**, probably requires a high degree of order in the transition state in which case steric effects should be important. Further study is needed to support these postulates.

The regiochemistry of the reaction is always *para* with respect to the nitro group with both 2- and 3-substituted nitrobenzenes. This preference is probably due to the bulkiness of the anion. Despite the fact that our base and solvent are those held responsible for the "*ortho* effect" in VNS *i.e. t* -BuOK/THF [87ACR282], no *ortho* substitution was observed.

Table 5.2. *p*-Diarylmethyl-*o*- and/or *m*-substituted Nitrobenzenes

5.7

5.7	X	Ar^1	Ar^2	Yield %
a	H	phenyl	phenyl	82
b	2-F	phenyl	phenyl	87
c	2-Cl	2-methoxyphenyl	4-methylphenyl	86
d	2-Cl	4-(*N,N*-dimethylamino)phenyl	phenyl	79
e	2-Cl	4-(*N,N*-dimethylamino)phenyl	3,4,5-trimethoxyphenyl	68
f	2-Br	4-methylphenyl	phenyl	52
g	2-Br	4-biphenyl	phenyl	38
h	2-MeO	phenyl	phenyl	68
i	2-MeO	4-chlorophenyl	phenyl	76
j	2-MeO	2-methylphenyl	phenyl	31
k	2-MeO	5-methylthien-2-yl	4-methoxyphenyl	28
l	2-MeO	4-(*N,N*-dimethylamino)phenyl	4-*n*-hexyloxyphenyl	48
m	2-Ph	4-biphenyl	phenyl	91
n	2-*t*-Bu	4-methoxyphenyl	phenyl	33
o	2-CF_3	4-(*N,N*-dimethylamino)phenyl	phenyl	50
p	2,3-$(CH)_4$	4-chlorophenyl	phenyl	94
q	3-F	4-methoxyphenyl	phenyl	56
r	3-MeO	4-chlorophenyl	phenyl	52

Oxidative nucleophilic substitution of hydrogen has previously been observed by Bernard with σ^H-adducts derived from benzotriazole stabilized anions and nitroarenes [95TL2169]. No systematic study of the factors that influence this process has been published so far. Attempts to measure the ratio of the VNS and ONSH products by GCMS were unsuccesful due to decomposition of the ONSH product. However, ^{1}H NMR allows quantitative evaluation of the ratio of the two products: the Csp^3–H bond in compound **5.7** gives a signal at 5.5–5.8 ppm while Csp^2–H in position 7 of the benzotriazolyl ring in compound **5.8** gives a signal at 6.5 ppm. By this means the ratios of the VNS and ONSH products could be quantified. When the quenching solution was degassed prior to its addition to the reaction mixture, only traces of ONSH product were observed. A study of the ONSH of benzotriazole bearing anionic σ-adducts is under way in this laboratory.

In conclusion, a general regiospecific method for synthesis of *p*-nitroaryl-diarylmethanes was developed starting from diarylmethanols and 2- and 3-substituted nitrobenzenes, making use of the quantitative reaction between benzotriazole and diarylmethanols under acidic catalysis and in the presence of perfluorocarbon fluids. In the presence of Brönsted or Lewis acids, diarylmethanols are highly electrophilic, reacting with electron-rich arenes in Friedel-Crafts fashion. In contrast, (diarylmethyl)benzotriazoles in the presence of strong bases are highly nucleophilic allowing reactions with electron poor arenes. Hence, our present VNS procedure complements Friedel-Crafts approaches to similar compounds, as pointed out by Makosza [92PJC3].

5.3 New Synthesis of *p*-Nitrophenyl Aryl Ketones

Oxidative nucleophilic substitution of hydrogen (ONSH) has been recently reviewed [92PJC3, 94T4913]. ONSH proceeds satisfactorily when the nucleophiles are resistant towards oxidation and when the equilibrium of the addition assures high concentrations of σ^H adducts **5.1** (Figure 5.1) and low concentrations of the nucleophile [96CC837]. The first ONSH with organolithiums was performed by Kienzle who

synthesized various mixtures of *o*- and *m*-alkyl nitroarenes from the corresponding alkyllithiums by an addition-oxidation sequence [78HCA449]. In Section 5.2 it has been described that during VNS involving benzotriazole-stabilized anions showed that the nucleophile is quite stable towards oxidation while the intermediate σ^H adducts are easily oxidized even by the air dissolved in the quenching solution. The regiochemistry of the reaction is always *para* to the nitro group therefore separation of the regioisomers would not be necessary.

Benzotriazole adduct of type **5.9** are readily available by the condensation of an aldehyde, triethyl orthoformate and benzotriazole [95JOC7619]. A route to *p*-nitro-benzophenone has been proposed according to Figure 5.4. The anions derived from **5.9** after deprotonation with *n*-BuLi are highly unstable and were trapped with the nitroarene after *ca.* 5 min at –78 °C. The σ^H complex **5.10** was stable for up to 5 hours at –78 °C and, upon oxidation gave a mixture of **5.9**, nitroarene and **5.11**. This shows that the transformation **5.9**→**5.10** is a reversible process. The highest observed conversion of **5.9** into **5.11** was 50%. Most likely, during the oxidation process, the hydrogen atom is transformed into an acidic proton that is transferred to the anion derived from **5.9**.

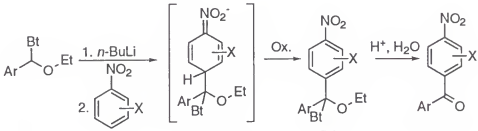


Figure 5.4

The synthesis of *p*-nitro-benzophenone **5.15** (Figure 5.5) has been accomplished by the deprotonation of adduct **5.13** and subsequent reaction with *o*-nitroanisole and oxidation with potassium permanganate:18-crown-6 to give **5.14** in 70% isolated yield while 50% of the starting material **5.13** was recovered. The hydrolysis of **5.14** went

smoothly with an ethanol-HCl 20% solution at room temperature for 2 days to give 3-methoxy-4-nitrophenyl phenyl ketone **5.15** in 95% isolated yield (Figure 5.5).

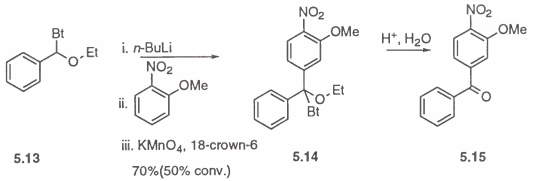


Figure 5.5

p-Nitrobenzophenones have been previously prepared by (i) the reaction of the arylcoppers with diazo-compounds [69CC515]; (ii) reaction of phenyldiazomethane with aromatic aldehydes in the presence of zinc iodide [81ACH309]; (iii) palladium coupling of allyltrialkyltin compounds with *p*-nitrobenzoyl chloride which gives a poor regioselectivity [83JOC4634] and the decarboxylation of α-alkyl-β-keto-β-(4-nitrophenyl)propionic acids obtained by the reaction of the polystyrene immobilized β-keto-β-(4-nitrophenyl) propionic acid enolate with alkyl halides [81JOC3756].

In conclusion, a new approach to *p*-nitro-benzophenones has been described. The new route is highly regiospecific and the starting materials are easily available.

5.4 Experimental Section

General Methods. Melting points were determined on a capillary melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^1H (300 MHz) or solvent as the internal standard for ^{13}C (75 MHz). Tetrahydrofuran was distilled under nitrogen immediately prior to use from sodium / benzophenone ketyl. Potassium *t*-butoxide was reagent grade purchased from Acros Organics and was handled in a dry box under nitrogen. All reactions involving potassium

t-butoxide and Grignard reagents were carried out under argon atmosphere. Column chromatography was conducted with silica gel 230-400 mesh. Compounds **5.2a-f** were reagent grade commercially available materials. Perfluorocarbon fluid (bp 104 °C) was purchased from 3M Co. 4-(*N*,*N*-Dimethylamino)phenylmagnesium bromide 1 M solution in THF was prepared according to literature procedure [94DP303].

5.4.1 Preparation of [4-(*N*,*N*-Dimethylamino)phenyll(phenyl)methanol (**5.2g**).

Sodium borohydride was added (0.83 g, 22 mmol) to a solution of 4-(*N*,*N*-dimethylamino)benzophenone (4.51 g, 20 mmol) in ethanol (50 mL). The mixture was stirred at rt for 6 hours, solvent was distilled off under reduced pressure and water (20 mL) and methylene chloride (30 mL) was added to the residue. The organic layer was separated, washed with water (20 mL) and brine (20 mL) and dried ($MgSO_4$). After solvent removal 4.50 g (98 %) product was obtained as a light green solid: mp 68–69 °C (lit.[46JCS797] mp 69–70 °C): ^{1}H NMR δ 2.42 (br s, 1H), 2.87(s, 6H), 5.68 (br s, 1H), 6.65 (d, J = 8.6 Hz, 2H), 7.15–7.22 (m, 3H), 7.26–7.35 (m, 4H); ^{13}C NMR δ 40.5 (2C), 75.8, 112.5 (2C), 126.3 (2C), 127.0, 127.7 (2C), 128.2 (2C), 132.1, 144.3, 150.0.

5.4.2 Preparation of (2-Methoxyphenyl)(4-methylphenyl)methanol (**5.2h**).

To a suspension of Mg (0.48 g, 0.02 mol) in THF (10 mL), 4-bromotoluene (2.07 g, 0.012 mol) was added. After 3 h reflux, the resulting cold solution (10 mL) was added to 2-methoxybenzaldehyde in THF (30 mL) at 0 °C and stirred under reflux for 5 h. The resulting mixture was treated with saturated aqueous ammonium chloride solution (40 mL) and extracted with methylene chloride (3 × 30 mL). The organic extract was dried ($MgSO_4$), solvent removed to yield an oil that was dissolved in ethanol (10 mL), sodium borohydride (0.019 g, 0.005 mol) was added and the mixture stirred at rt for 5 h. The solvent was removed under reduced pressure, water (20 ml) was added and extracted with methylene chloride (2 × 20 mL). The organic extract was washed with water (2 × 20 mL),

brine (10 mL) and solvent removed to yield an oil that was subjected to column chromatography with hexanes:diethyl ether (3:1) to give 2.02 g (88%) colorless oil; ^{1}H NMR δ 2.30 (s, 3H), 3.09 (s, 1H), 3.73 (s, 3H), 5.98 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 7.09 (d, J = 8.0 Hz, 2H), 7.19–7.25 (m, 4H); ^{13}C NMR δ 21.0, 55.2, 71.8, 110.6, 120.6, 126.4 (2C), 127.6, 128.4, 128.7 (2C), 132.1, 136.6, 140.3, 156.6. Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.32; H, 7.26.

5.4.3 General Procedure for the Preparation of Compounds **5.2i** and **5.2j**.

To a solution of the appropriate aldehyde (20 mmol) in dry THF (30 mL), a solution of 4-(*N*,*N*-dimethylamino)phenylmagnesium bromide in THF (1 M, 20 mL, 20 mmol) was added with stirring and cooling at 0 °C. After 10 h reflux, the solution was treated with saturated aqueous ammonium chloride solution (40 mL), extracted with methylene chloride (2 × 50 mL), the combined organic layer washed with NaOH (5%, 2 × 20 mL) and brine (20 mL) and dried ($MgSO_4$). The solvent was removed to give an oil that was dissolved in ethanol (20 mL), $NaBH_4$ (0.38 g, 10 mmol) added and stirred at rt for 1 h. The solvent was removed, the remaining oil was treated with water (50 mL), extracted with methylene chloride (3 × 50 mL), dried ($MgSO_4$), and the solvent removed to give an oil that was recrystallized from the appropriate solvent.

[4-(*N*,*N*-Dimethylamino)phenyl, 4-(*n*-hexyloxy)phenyl]methanol (**5.2i**).

3.55 g (56 %) white needles: mp 62–64 °C (hexanes:methylene chloride); ^{1}H NMR δ 0.87–0.92 (t, J = 6.4 Hz, 3H), 1.31–1.45 (m, 6H), 1.69–1.76 (m, 2H), 2.46 (d, J = 2.4 Hz, 1H), 2.87 (s, 6H), 3.89 (t, J = 6.5 Hz, 2H), 5.63 (s, 1H), 6.65 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.5 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 14.0, 22.5, 25.6, 29.2, 31.5, 40.5 (2C), 67.9, 75.3, 112.4 (2C), 114.1 (2C), 127.5 (2C), 127.5 (2C), 132.4, 136.4, 149.9, 158.1. Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.03; H, 8.93; N, 4.28. Found: C, 77.02; H, 9.06; N, 4.18.

[4-(*N*,*N*-Dimethylamino)phenyl](3,4,5-trimethoxyphenyl) methanol (**5.2j**).

4.64 g (73 %) white solid: mp 139–141 °C (methanol); ^{1}H NMR δ 2.32 (br s, 1H), 2.92 (s, 6H), 3.82 (s, 9H), 5.67 (s, 1H), 6.62 (s, 2H), 6.68 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR δ 40.4 (2C), 55.9 (2C), 60.6, 75.7, 103.3 (2C), 112.4 (2C), 127.5 (2C), 131.8, 136.7, 140.0, 150.0, 152.9 (2C). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.05; H, 7.50; N, 4.33.

5.4.4 Preparation of (4-Methoxyphenyl)(5-methyl-2-thienyl)methanol (**5.2k**).

To a solution of 2-methylthiophene (1.96 g, 20 mmol) in THF (80 mL) at –40 °C, *n*-BuLi (2 M, 10.5 mL, 21 mmol) was added. After 30 min stirring, the temperature was lowered to –78 °C and *p*-anisaldehyde (2.72 g, 20 mmol) in THF (20 mL) was added. The mixture was allowed to warm to rt, treated with saturated aqueous ammonium chloride solution (90 mL) and extracted with methylene chloride (2 × 50 mL). The organic layer was washed with NaOH solution (5%, 2 × 50 mL), brine (2 × 50 mL) and water (2 × 50 mL), dried ($MgSO_4$), solvent was removed to give an oil that was recrystallized from diethyl ether-hexanes to yield 2.21g (47 %) of white solid: mp 67.5–68.0 °C; ^{1}H NMR δ 2.40 (s, 3H), 2.68 (s, 1H), 3.76 (s, 3H), 5.83 (s, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 6.84 (d, *J* = 8.7 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR δ 15.2, 55.1, 71.2, 113.7 (2C), 124.5, 124.5, 127.4 (2C), 135.5, 139.8, 146.0, 159.1. Anal. Calcd for $C_{13}H_{14}OS$: C, 66.64; H, 6.02. Found: C, 66.73; H, 6.25.

5.4.5 General Procedure for Preparation of Compounds **5.7a-o** and **5.8r**.

The mixture of corresponding diphenylmethanol (2 mmol), benzotriazole (0.31 g, 2.6 mmol), *p*-toluenesulfonic acid monohydrate (0.042 g, 0.2 mmol) (no catalyst was used for the preparation of compounds **5.3e**, **g–k**) and performance fluid (bp 104 °C) (20 mL) was refluxed overnight. The performance fluid was removed on cooling and the remaining oil was dissolved in methylene chloride (20 mL), the solution washed with NaOH solution

(5%, 2 × 20 mL), brine (20 mL), water (20 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give a solid that was mixed with the appropriate nitroarene (2 mmol) air replaced with argon and dissolved in THF (10 mL). The solution was added dropwise *via* a cannula (over 40 min) to a solution of potassium *tert*-butoxide (1.12 g, 10 mmol) in THF (10 mL) at –20 °C with stirring. After an additional 4 h stirring at –20 °C, saturated aqueous ammonium chloride solution (30 mL) was added and when the deep red color disappeared the reaction mixture was extracted with methylene chloride (3 × 20 mL). The organic layer was dried ($MgSO_4$) and solvent removed under reduced pressure. The remaining oil was dissolved in methylene chloride (40 mL), washed with NaOH solution (5%, 20 mL), brine (2 × 20 mL) and water (20 mL), dried ($MgSO_4$), the solvent was removed under reduced pressure and the residual oil subjected to column chromatography.

1-Benzhydryl-4-nitrobenzene (**5.7a**).

Hexanes:diethyl ether (3:1) was used as the eluent to give yellow plates: mp 95-97 °C (hexanes) (lit [49JA2209] mp 93 °C); ^{1}H NMR δ 5.63 (s, 1H), 7.09 (d, J = 6.9 Hz, 4H), 7.25–7.34 (m, 8H), 8.14 (d, J = 8.5 Hz, 2H); ^{13}C NMR δ 56.6, 123.5, 126.9, 128.6, 129.3, 130.2, 142.3, 145.5, 151.6.

4-Benzhydryl-2-fluoro-1-nitrobenzene (**5.7b**).

Hexanes:diethyl ether (3:1) was used as the eluent to give yellow plates: mp 59-60 °C (hexanes); ^{1}H NMR δ 5.58 (s, 1H), 6.99–7.10 (m, 6H), 7.25–7.36 (m, 6H), 7.99 (t, J = 7.8 Hz, 1H); ^{13}C NMR δ 56.5, 119.0 (d, J = 21.2 Hz, 1C), 125.5 (d, J = 37.6 Hz, 1C), 127.2 (2C), 128.8 (4C), 129.2 (4C), 141.6 (2C), 153.7 (d, J = 18.4 Hz, 1C), 155.4 (d, J = 275.0 Hz, 1C). Anal. Calcd for $C_{19}H_{14}FNO_2$: C, 74.26; H, 4.59; N, 4.56. Found: C, 74.36; H, 4.73; N, 4.66.

2-[(3-Chloro-4-nitrophenyl)(4-methylphenyl)methyl]phenyl methyl ether (**5.7c**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an yellow oil; ^{1}H NMR δ 2.33 (s, 3H), 3.72 (s, 3H), 5.86 (s, 1H), 6.80 (d, J = 6.4 Hz, 1H), 6.86–6.95 (m, 4H), 7.08–7.12 (m, 3H), 7.22–7.28 (m, 2H), 7.77 (d, J = 8.5Hz, 1H); ^{13}C NMR δ 21.0, 49.0, 55.4, 110.7, 120.5, 125.4, 127.0, 128.3, 128.4, 129.3 (4C), 130.0, 130.5, 132.3, 136.5, 138.5, 145.8, 151.3, 156.8. Anal. Calcd for $C_{21}H_{18}NO_3Cl$: C, 68.57; H, 4.93; N, 3.81. Found: C, 68.38; H, 5.07; N, 3.87.

*N*1,*N*1-Dimethyl-4-[(3-chloro-4-nitrophenyl)(phenyl)methyl]aniline (**5.7d**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an orange oil; ^{1}H NMR δ 2.93 (s, 6H), 5.46 (s, 1H), 6.67 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.5 Hz, 2H), 7.07–7.15 (m, 3H), 7.22–7.33 (m, 4H), 7.78 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 40.4 (2C), 55.4, 112.5 (2C), 125.5, 126.8, 127.1, 128.4, 128.6 (2C), 129.1 (2C), 129.3, 129.8 (2C), 132.5, 142.4, 145.8, 149.4, 151.6. Anal. Calcd for $C_{21}H_{19}ClNO_2$: C, 68.76; H, 5.22; N, 7.64. Found: C, 68.91; H, 5.45; N, 7.62.

N-[4-[(3-Chloro-4-nitrophenyl)(3,4,5-trimethoxyphenyl)methyl]phenyl]-*N*1,*N*1-dimethyl aniline (**5.7e**).

Hexanes:diethyl ether (3:1) was used as the eluent to give orange prisms, mp 58–60 °C: ^{1}H NMR δ 2.95 (s, 6H), 3.75 (s, 6H), 3.84 (s, 3H), 5.40 (s, 1H), 6.30 (s, 2H), 6.68 (d, J = 8.6 Hz, 2H), 6.94 (d, J = 8.5 Hz, 2H), 7.15–7.17 (m, 1H), 7.31 (s, 1H), 7.81 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 40.4 (2C), 55.6, 56.1 (2C), 60.8, 106.4 (2C), 112.5 (2C), 125.5, 127.1, 128.3, 129.1, 129.7 (2C), 132.4, 136.8, 138.0, 145.8, 149.5, 151.5, 153.3 (2C). Anal. Calcd for $C_{24}H_{25}N_2O_5Cl$: C, 63.09; H, 5.51; N, 6.13. Found: C, 63.06; H, 5.51; N, 6.00.

2-Bromo-4-[(4-methylphenyl)(phenyl)methyl]-1-nitrobenzene (**5.7f**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an orange oil; ^{1}H NMR δ 2.31 (s, 3H), 5.51 (s, 1H), 6.95 (d, J = 8.0 Hz, 2H), 7.05–7.32 (m, 8H), 7.48 (d, J = 1.5 Hz, 1H), 7.73 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 20.9, 55.7, 114.5, 125.5, 127.0,

128.7 (2C), 129.0 (3C), 129.1 (2C), 129.4 (2C), 135.6, 136.7, 138.7, 141.9, 147.8, 150.7. Anal. Calcd for $C_{20}H_{16}BrNO_2$: C, 62.84; H, 4.22; N, 3.66. Found: C, 62.45; H, 4.30; N, 3.80.

4-Benzhydryl-2-bromo-1-nitrobenzene (**5.7g**).

Hexanes:diethyl ether (3:1) was used as the eluent to give orange prisms: mp 59–61 °C; ^{1}H NMR δ 5.57 (s, 1H), 7.09–7.43 (m, 11H), 7.52–7.57 (m, 5H), 7.75 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 55.8, 114.7, 125.6, 127.0 (2C), 127.2, 127.4 (3C), 128.8 (4C), 129.1, 129.2 (2C), 129.6 (2C), 135.7, 140.0, 140.3, 140.7, 141.6, 147.9, 150.4. Anal. Calcd for $C_{25}H_{18}BrNO_2$: N, 3.15. Found: N, 3.21.

4-Benzhydryl-2-methoxy-1-nitrobenzene (**5.7h**).

Hexanes:diethyl ether (3:1) was used as the eluent to give orange prisms: mp 142–144 °C (methanol); ^{1}H NMR δ 3.80 (s, 3H), 5.58 (s, 1H), 6.75 (dd, J_1= 8.4 Hz, J_2 = 1.0 Hz, 1H), 6.83 (s, 1H), 7.09 (d, J = 6.8 Hz, 4H), 7.22–7.36 (m, 6H), 7.78 (d, J = 8.5 Hz, 1H); ^{13}C NMR δ 56.2, 56.7, 114.6, 121.2, 125.6, 126.8 (2C), 128.5 (4C), 129.2 (4C), 137.7, 142.2 (2C), 151.4, 153.0. Anal. Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.17; H, 5.30; N, 4.23.

4-[(4-Chlorophenyl)(phenyl)methyl]-2-methoxy-1-nitrobenzene (**5.7i**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an orange oil; ^{1}H NMR δ 3.80 (s, 3H), 5.55 (s, 1H), 6.72 (dd, J = 8.5 Hz, 1.4 Hz, 1H), 6.82 (d, J =1.4 Hz, 1H), 7.03 (d, J = 8.3 Hz, 2H), 7.06–7.09 (m, 2H), 7.25–7.34 (m, 5H), 7.77 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 56.1, 56.3, 114.5, 121.1, 125.8, 127.1, 128.7 (4C), 129.1 (2C), 130.6 (2C), 132.7, 137.9, 140.8, 141.7, 150.8, 153.1. Anal. Calcd for $C_{20}H_{16}ClNO_3$: C, 67.90; H, 4.56; N, 3.96. Found: C, 67.52; H, 4.60; N, 4.11.

2-Methoxy-4-[(2-methylphenyl)(phenyl)metyl]-1-nitrobenzene (**5.7j**).

Hexanes:diethyl ether (3:1) was used as the eluent to give yellow prisms: mp 126–127 °C; ^{1}H NMR δ 2.21 (s, 3H), 3.76 (s, 3H), 5.70 (s, 1H), 6.69 (dd, J = 8.5 and 1.7 Hz, 1H), 6.76 (d, J = 1.1 Hz, 1H), 6.79 (s, 1H), 7.03 (d, J = 6.7 Hz, 2H), 7.13–7.29

(m, 6H), 7.75 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 19.8, 53.5, 56.2, 114.6, 121.4, 125.6, 125.9, 126.8, 126.9, 128.5 (2C), 129.0, 129.3 (2C), 130.6, 136.5, 137.7, 140.7, 141.7, 151.1, 153.0. Anal. Calcd for $C_{21}H_{19}NO_3$: C, 75.66; H, 5.74; N, 4.20. Found: C, 75.63; H, 5.89; N, 4.14.

2-[(3-Methoxy-4-nitrophenyl)(2methoxyphenyl)metyl]-5-methyl-thiophene (**5.7k**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an yellow oil; ^{1}H NMR δ 2.44 (s, 3H), 3.81 (s, 3H), 3.87 (s, 3H), 5.59 (s, 1H), 6.49 (d, J = 3.3 Hz, 1H), 6.61 (d, J = 2.5 Hz, 1H), 6.88 (d, J = 8.5 Hz, 3H), 6.96 (s, 1H), 7.13 (d, J = 8.5 Hz, 2H), 7.80 (d, J = 8.2 Hz, 1H); ^{13}C NMR δ 15.2, 51.4, 55.2, 56.3, 113.9 (3C), 120.6, 124.7, 125.8, 126.4, 129.6 (2C), 134.4, 137.8, 139.6, 143.8, 151.5, 153.1, 158.6. Anal. Calcd for $C_{20}H_{19}NO_4S$: C, 65.02; H, 5.18; N, 3.79. Found: C, 65.37; H, 5.26; N, 3.70.

N-{4-[[4-(hexyloxy)phenyl](3-methoxy-4-nitrophenyl)methyl]phenyl}-*N*1, *N*1-dimethyl aniline (**5.7l**).

Hexanes:diethyl ether (4:1) was used as the eluent to give an yellow oil: ^{1}H NMR d 0.85–0.91 (t, J = 6.6 Hz, 3H), 1.27–1.47 (m, 6H), 1.71–1.78 (m, 2H), 2.90 (s, 6H), 3.79 (s, 3H), 3.91 (t, J = 6.4 Hz, 2H), 5.41 (s, 1H), 6.65 (d, J = 8.7 Hz, 2H), 6.75 (d, J = 8.3 Hz, 1H), 6.81 (d, J = 8.5 Hz, 2H), 6.85 (s, 1H), 6.93 (d, J = 8.5 Hz, 2H), 6.98 (d, J = 8.5 Hz, 2H), 7.74 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 13.9, 22.5, 25.6, 29.2, 31.5, 40.4 (2C), 55.2, 56.2, 67.9, 112.4 (2C), 114.3 (2C), 114.4, 121.2, 125.5, 129.7 (2C), 130.0 (2C), 130.3, 134.9, 137.5, 149.2, 152.8, 153.0, 157.8. Anal. Calcd for $C_{28}H_{34}N_2O_4$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.73; H, 7.64; N, 6.23.

4-[(4-(Biphenylyl)(phenyl)methyl]-2-phenyl-1-nitrobenzene (**5.7m**).

Hexanes:diethyl ether (5:1) was used as the eluent to give yellow prisms: mp 55–57 °C; ^{1}H NMR δ 5.65 (s, 1H), 7.14–7.43 (m, 18H), 7.55 (t, J = 7.5 Hz, 3H), 7.78 (d, J = 8.4 Hz, 1H); ^{13}C NMR δ 56.2, 124.3, 127.0 (2C), 127.3 (2C), 127.9 (2C), 128.1, 128.6 (2C), 128.7 (2C), 128.8 (2C), 129.0, 129.3 (2C), 129.7 (2C), 131.9, 132.2 (2C), 132.9,

136.4, 137.4, 139.7, 140.5, 141.4, 147.5, 149.0. Anal. Calcd for $C_{31}H_{23}NO_2$: C, 84.33; H, 5.25; N, 3.17. Found: C, 83.95; H, 5.50; N, 3.35.

2-(*tert*-Butyl)-4-[(4-methoxyphenyl)(phenyl)methyl]-1-nitrobenzene (**5.7n**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an yellow oil; ^{1}H NMR δ 1.32 (s, 9H), 3.79 (s, 3H), 5.51 (s, 1H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.98–7.01 (m, 3H), 7.07 (d, *J* = 7.4 Hz, 2H), 7.22–7.33 (m, 5H); ^{13}C NMR δ 30.6 (3C), 35.6, 55.2, 55.8, 113.9 (2C), 123.9, 126.6, 127.6, 128.5 (2C), 129.2 (2C), 129.7, 130.2 (2C), 134.9, 141.3, 143.2, 147.2, 149.5, 158.3. Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.78; H, 6.82; N, 3.81.

*N*1,*N*1-Dimethyl-4-[[4-nitro-3-(trifluoromethyl)phenyl](phenyl)methyl]aniline (**5.7o**).

Hexanes:diethyl ether (3:1) was used as the eluent to give orange prisms: mp 86–88 °C; ^{1}H NMR δ 2.90 (s, 6H), 5.55 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 2H), 6.93 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 7.3 Hz, 2H), 7.22–7.32 (m, 3H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.62 (s, 1H), 7.74 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 40.3 (2C), 55.5, 112.5 (2C), 122.0 (q, *J* = 271.9 Hz, 1C), 123.4 (q, *J* = 33.5 Hz, 1C), 125.1, 126.9, 128.6 (3C), 129.1 (2C), 129.8 (2C), 133.5, 142.3, 146.1, 149.5, 150.9. Anal. Calcd for $C_{22}H_{19}F_3N_2O_2$: C, 65.99; H, 4.78; N, 7.00. Found: C, 66.23; H, 4.84; N, 7.05.

1-[(4-Chlorophenyl)(phenyl)methyl]-4-nitronaphthalene (**5.7p**).

Hexanes:diethyl ether (3:1) was used as the eluent to give yellow plates: mp 70–74 °C; ^{1}H NMR δ 6.27 (s, 1H), 7.00–7.07 (m, 5H), 7.24–7.34 (m, 5H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.4 Hz, 1H), 8.02–8.09 (m, 2H), 8.52 (d, *J* = 8.8 Hz, 1H); ^{13}C NMR δ 52.9, 56.3, 122.9, 123.7, 124.8, 125.4, 126.0, 127.2, 127.7, 128.8 (4C), 129.4 (2C), 130.8 (2C), 132.5, 132.9, 141.0, 141.9, 146.2, 146.5. Anal. Calcd for $C_{23}H_{16}ClNO_2$: C, 73.90; H, 4.31; N, 3.75. Found: C, 73.77; H, 3.96; N, 3.59.

2-Fluoro-1-[(4-methoxyphenyl)(phenyl)methyl]-4-nitrobenzene (**5,7q**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an yellow oil; ^{1}H NMR δ 3.76 (s, 3H), 5.81 (s, 1H), 6.84 (d, J = 8.7 Hz, 2H), 6.98 (d, J = 8.7 Hz, 2H), 7.06–7.15 (m, 3H), 7.24–7.32 (m, 3H), 7.86–7.93 (m, 2H); ^{13}C NMR δ 48.8, 55.2, 111.2 (d, J = 27.6 Hz, 1C), 111.3, 114.0 (2C), 119.0, 127.0, 128.6 (2C), 129.0 (2C), 130.1 (2C), 131.3 (d, J = 3.5 Hz, 1C), 132.9, 139.4 (d, J = 14.2 Hz, 1C), 141.3, 147.3 (d, J = 8.6 Hz, 1C), 158.6, 159.9 (d, J = 250.4 Hz, 1C). Anal. Calcd for $C_{20}H_{16}FNO_3$: C, 71.21; H, 4.78; N, 4.15. Found: C, 71.14; H, 4.88; N, 4.14.

1-[(4-Chlorophenyl)(phenyl)methyl]-2-methoxy-4-nitrobenzene (**5,7r**).

Hexanes:diethyl ether (3:1) was used as the eluent to give an yellow oil; ^{1}H NMR δ 3.80 (s, 3H), 5.90 (s, 1H), 6.96-7.05 (m, 5H), 7.22–7.30 (m, 5H), 7.71–7.75 (m, 2H); ^{13}C NMR δ 49.2, 56.0, 105.4, 115.5, 126.8, 128.5 (4C), 129.1 (2C), 130.3, 130.5 (3C), 132.3, 139.7, 140.8, 141.6, 147.6, 157.2. Anal. Calcd for $C_{20}H_{16}ClNO_3$: C, 67.90; H, 4.56; N, 3.96. Found: C, 67.99; H, 4.54; N, 3.95.

1-[(4-Chlorophenyl)(2-methoxy-4-nitrophenyl)(phenyl)methyl]-1*H*-1,2,3-benzotriazole (**5,8r**)

Hexanes:diethyl ether (3:1) was used as the eluent to give yellow microcrystals: mp 124–126 °C; ^{1}H NMR δ 3.38 (s, 3H), 6.54 (d, J = 8.5 Hz, 1H), 7.06–7.19 (m, 6H), 7.25-7.31 (m, 6H), 7.72 (d, J = 1.7 Hz, 1H), 7.79 (dd, J = 1.9, 8.6 Hz, 1H), 8.05 (d, J = 8.3 Hz, 1H); ^{13}C NMR δ 55.8, 76.7, 107.5, 112.7, 115.0, 120.1, 123.7, 127.0, 127.9 (2C), 128.0 (2C), 128.3, 129.4 (2C), 129.8, 131.1 (2C), 133.5, 134.0, 137.6, 138.0, 139.0, 146.5, 149.3, 158.8. Anal. Calcd for $C_{26}H_{19}ClN_4O_3$: N, 11.90. Found: N, 11.77.

Preparation of 1-[(Ethoxy)(3-methoxy-4-nitrophenyl)(phenyl)methyl]-1*H*-1,2,3-benzotriazole **5.14**.

1-[(Ethoxy)(phenyl)methyl]-1*H*-benzotriazole **5.13** (0.507g, 2 mmol) was dissolved in THF (50 mL) and cooled at –78 °C. *n*-BuLi solution in hexanes (1.6 *M*, 1.25 mL, 2 mmol) was added followed after 5 min by the addition of 2-nitroanisole (0.310g, 2 mmol). After 2 hours at –78 °C, a slurry of potassium permanganate (0.209g, 1.3 mmol) and 18-crown-6 (0.309g, 1.3 mmol) in THF (20 mL) was added. The reaction mixture was allowed to warm at rt overnight, was washed with brine (3 × 30 mL), the solvent was under reduced pressure and the remaining oil subjected to column chromatography. yield 0.283 g (colorless prisms, 70% for a 50% conversion of **5.13**) mp 95.6-97.1 °C; ^{1}H NMR δ 1.18 (t, *J* = 6.9 Hz, 3H), 3.11–3.31 (m, 2H), 3.90 (s, 3H), 6.91 (d, *J* = 8.0 Hz, 1H), 7.28–7.45 (m, 8H), 7.61 (d, *J* = 5.0 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR δ 14.7, 56.6, 60.4, 112.6, 112.9, 119.1, 120.1, 124.4, 125.6, 127.2, 127.8, 128.6, 129.0, 133.3, 139.2, 146.5, 147.4, 152.8. Anal. Calcd for $C_{22}H_{20}N_4O_4$: H, 4.98; N, 13.85. Found: H, 5.01; N, 13.65.

Preparation of 3-methoxy-4-nitro-benzophenone **5.15**.

Compound **5.14** (0.202g, 0.5 mmol) was dissolved in ethanol (2 mL) and hydrochloric acid (6 *N*, 1 mL). The reaction mixture was stirred at rt for 2 days. The solvents were removed under reduced pressure, the remaining solid dissolved in methylene chloride (20 mL) and washed with sodium hydroxide (5%, 3 × 20 mL), water (4 × 20 mL), was dried ($MgSO_4$) and solvent was removed under reduced pressure: yield 0.122 g (colorless prisms, 95%) mp 121.3-123.2 °C: ^{1}H NMR δ 4.01 (s, 3H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.49–7.55 (m, 3H), 7.65 (t, *J* = 7.1 Hz, 1H), 7.81 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR δ 56.8, 114.5, 121.8, 125.1, 128.6, 130.0, 133.3, 142.3, 152.7, 194.6. Anal Calcd for $C_{14}H_{11}NO_2$: C, 65.37; H, 4.31; N, 5.44. Found: C, 65.80; H, 4.58; N, 5.33.

CHAPTER 6
PERFORMANCE FLUIDS AS AN INERT MEDIUM FOR THE PREPARATION OF BENZOTRIAZOLE DERIVATIVES

6.1 Introduction

Organic reactions can be carried out either in the presence or absence of a solvent. An important reason for using a solvent is to limit the reaction temperature to its boiling point. If reactions are heated without a solvent for a prolonged period, two problems often arise: (i) the reaction components are more easily oxidized in the absence of the protection provided by the solvent vapor; (ii) the desired constant reaction temperature is sometimes difficult to maintain.

Condensation reactions such as ester, acetal, imine, or enamine formation are synthetically important and a significant effort has been made for improving the conversion and yields for these reactions (for a recent discussion see [94SC583]). Recently, Zhu reported the use of perfluorocarbon (PFC) fluids (performance fluids) as the inert medium for ester transformations as well as for acetal, ketal and enamine syntheses [93S953]. Performance fluids provide a novel medium in which the substrates react as though in the absence of solvent, but the reaction proceeds as though in the presence of solvent with respect to maintenance of temperature and protection by the solvent vapor. The basic device for running reactions in the presence of performance fluids is shown in Figure 6.1: the mixture of reagents (which have to be molten at the boiling temperature of the performance fluid) is put in a flask equipped with a magnetic stirrer bar and on top of it a "reversed Dean-Stark" device available from Ace Glass is mounted. The trap retains the less dense polar fluid allowing for the condensed performance fluid (with a density higher than 1.5 g/mL) to return to the reaction flask. The reactions are heterogeneous due to the insolubility

of the reagents and products in the performance fluids. It is shown here that some benzotriazole derivatives are conveniently prepared in performance fluids and the characteristics of the performance fluids makes possible reactions with an unfavorable thermodynamic equilibrium.

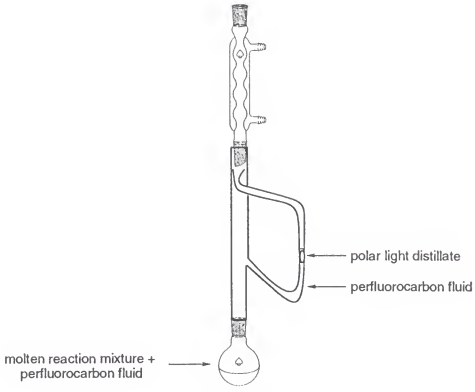


Figure 6.1

6.2 Benzotriazole Adducts of Aldehydes with Amides and Amines

Recent publications from our laboratory have demonstrated the synthetic utility of benzotriazole adducts of types **6.5** and **6.6** as intermediates for the preparation of amines and amides [91T2683]. The preparation of adducts of types **6.5** and **6.6** from aldehydes, benzotriazole and amines or amides is usually carried out in benzene or toluene by the Dean-Stark method [87JCS(P1)799, 93JOC2086, 89JCS(P1)225]. Although many of these preparations gave good results, several limitations such as occasional low yields, and the long reaction times (up to 72 hours) required for preparation of amide derivatives **6.6** by the normal Dean-Stark method [93JOC2086] were evident. An improved and more

powerful method of water-removal using performance fluids as an inert medium in conjunction with a reversed Dean-Stark trap is here described.

Performance fluids belong to classes of perfluorinated and saturated aliphatic compounds such as perfluoroalkanes or perfluoroalkyl ethers. They have a high density and are immiscible with water and organic compounds[93S953](they have limited solubility in hexanes). Our reactions were carried out in either PFC 5070 (bp 82 °C) or PFC 5080 (bp 104 °C). In general, the starting materials were mixed and heated under reflux with a reversed Dean-Stark trap. The denser phase, PFC, returned to the reaction mixture and water remained in the trap. The reactants, including benzotriazole, were

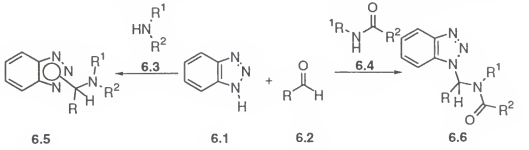


Figure 6.2

Table 6.1 Preparative Data of Benzotriazole Derivatives **6.5** and **6.6**

	Product							Literature			
Cpd	R	R^1	R^2	PF	Time (hrs)	Yield (%)	mp (°C)	Method	Time (hrs)	mp (°C)	Yield (%)
6.5a	Ph	H	pyridin-2-yl	5070	3	98		A[a]	4	148-150	75
6.5b	*i*-Pr	H	4-$CH_3C_6H_4$	5070	3	95					
6.6a	4-$O_2NC_6H_4$	H	Ph	5080	6	97	225-227	C[b]	24	219-221	81
6.6b	H	H	4-$CH_3C_6H_4$	5070	2	95	176-177	D[a]	32	181-182	32
6.6c	H	H	NH_2	5080	2	97	187-189				
6.6d	Ph		$-(CH_2)_3-$	5070	3	95	94-96				
6.6e	*i*-Pr		$-(CH_2)_3-$	5080	4	92	133-135				
6.6f	H		$-(CH_2)_3-$	5070	2	95	82-83	B[c]	24	78-80	96
6.6g	Ph		$-(CH_2)_4-$	5080	4	52[d]					
6.6h	*i*-Pr		$-(CH_2)_4-$	5080	5	77[d]	111-112				
6.6i	*i*-Pr		$-(CH_2)_5-$	5080	5	44[d]	113-114				
6.6j	H	Me	Ph	5080	2	80	98-99	C[c]	48	111-112	80

a) Unpublished work in our group. *b)* [91JOC4439]. *c)* [93JOC2086]. *d)* Yields after recrystallization. Methods: A = Dean-Stark with benzene; B = reflux in AcOH; C = Dean-Stark with toluene and TsOH as catalyst, D = Benzotriazole, paraformaldehyde and *p*-toluonitrile.

Table 6.2. ^{13}C NMR Spectral Data of Compounds **6.5** and **6.6** (ppm)

Cpd	Benzotriazole						C=O	NCH_2Bt or NCHBt	R	R^1	R^2
	C4	C5	C6	C7	C7a	C3a					
6.5a[a]	119.9	124.0	129.5	110.6	131.9	147.9	-	69.1	126.4, 128.9, 131.9, 137.0	-	155.8, 148.8, 148.2, 137.3, 137.9
	119.6	129.0	129.0	119.6	146.2	146.2					
6.5b[a]	120.1	126.1	127.6	110.2	129.8	143.7	-	81.65	19.1, 19.4, 35.1, 18.5, 18.7, 34.5	-	20.2, 19.4
	118.2	129.7	129.7	118.2	142.5	142.5		76.57			
6.6a[b]	119.9	124.1	128.3	111.5	132.6	145.7	167.4	65.6	148.2, 145.8, 143.7, 133.2	-	132.7, 128.4, 122.2, 128.8
6.6b	119.2	124.3	129.2	111.2	132.5	145.9	167.7	51.5	-	-	21.4, 127.4, 127.9, 129.9, 142.9
6.6c[b]	118.9	124.0	127.2	111.4	132.0	145.3	156.7	52.6	-	-	-
6.6d	119.4	124.5	128.9	110.8	132.6	144.8	175.3	65.8	127.0, 127.9, 128.9, 134.1	17.7, 30.1, 44.1	
6.6e	119.1	123.9	127.4	109.8	132.9	144.9	175.2	68.3	18.6, 18.3, 28.2	28.2, 30.3, 42.0	
6.6f	119.2	124.1	127.7	110.2	131.8	145.7	175.3	53.4	-	45.6, 30.1, 17.2	
6.6g[a]	119.6	124.2	127.7	110.1	133.4	145.1	171.0	66.2	133.9, 128.7, 128.6, 127.1	20.7, 22.8, 22.9, 32.2, 32.4, 44.1, 44.7	
	118.4	133.9	133.9	118.4	143.9	143.9		74.2			
6.6h	119.3	124.2	127.7	110.5	133.4	145.3	170.7	69.3	27.6, 18.3, 19.0	32.1, 22.6, 27.6, 41.5	
6.6i	119.5	124.3	127.7	110.4	133.3	145.3	176.5	70.3	28.4, 18.6, 19.0	29.41, 23.0, 28.4, 37.0, 42.8	
6.6j	119.5	124.2	128.3	110.9	132.2	145.9	171.8	57.8	-	36.2	134.4, 130.3, 127.8, 126.9

a) Mixture of 1- and 2-benzotriazolyl derivatives. *b)* In DMSO-d_6.

Table 6.3. ^{1}H NMR Spectral Data of Compounds **6.5** and **6.6** [(ppm), J(Hz)]

Cpd	Benzotriazole				NH	NCH_2Bt or NCHBt	R	R^1	R^2
	H^4	H^5	H^6	H^7					
6.5a[a,b]	8.52 (d, 7.5)	8.07[c]	7.75 (t, 7.5)	8.02[c]	6.24(d, 8.1, 1H)	6.60-6.80 (m, 1H)	7.27-7.5 (m, 9H)		
6.5b[b,d]	8.02 (d, 7.4)	7.40 (t, 8.1)	7.37-7.4[c]	7.69 (d,7.4)	4.70, 4.93 (d,10.1, 1H)	5.90-6.02 (m, 1H)	0.78 (d, 7.3, 3H) 1.23 (d, 7.3, 3H)	4.71 (s, 1H)	2.16 (s, 3H), 6.6 (d, 8.1, 2H), 6.9 (d, 8.1, 2H)
6.6a	8.43 (d, 8.1)	8.01 (t, 8.1)	8.05 (t, 8.1)	8.14 (d, 8.1)	10.5 (d, 8.5,1H)	8.00[c] (d, 8.5, 1H)	8.33 (d, 8.5, 2H) 7.75 (d, 8.5, 2H)	-	7.43-7.53 (m, 5H)
6.6b	8.03 (d, 7.5)	7.34 (t, 7.5)	7.48 (t, 7.5)	7.96 (d, 8.3)	8.39 (t, 6.7)	6.31(d, 6.7, 2H)	-	8.39 (t, 6.7, 1H)	2.34 (s, 3H), 7.18 (d, 8.3, 2H), 7.83 (d, 8.3, 2H)
6.6c	8.02 (d, 7.4)	7.38 (t, 8.1)	7.47 (t, 7.7)	7.95 (d, 8.6)	7.77 (t, 6.4)	6.03(d, 6.4, 2H)	-	-	6.8-6.9 (m, 2H)
6.6d	8.10 (d, 7.2)	7.39[c]	7.46[c]	7.55 (d, 8.4)	-	8.08[c](s, 1H)	7.18-7.21 (m, 2I1), 7.36-7.47 (m, 3H)	2.01-2.08 (m, 2H), 2.40-2.60 (m, 2H), 3.44-3.49 (m, 1H), 3.66-3.72 (m, 1H)	
6.6e	8.06 (d, 8.4)	7.39 (t, 7.1)	7.51 (t, 7.1)	7.83 (d, 8.3)	-	6.40(d, 11.0, 2I1)	3.60-3.67 (m, 1H), 1.15 (d, 6.7, 3H), 0.86 (d, 6.7, 3H)	3.20-3.32 (m, 2H), 1.80-2.12 (m, 2H), 2.20-2.44 (m, 2H)	
6.6f	8.03 (d, 8.3)	7.39 (t, 7.4)	7.51 (t, 7.1)	7.96 (d, 8.3)	-	6.10 (s, 2H)	-	3.46 (t, 7.1, 2H), 2.41 (t, 7.9, 2H), 2.00 (quintet, 7.6, 2H)	
6.6g[b,e]	8.10 (d, 8.4)	7.48 (t, 7.1)	7.35[c]	7.67 (d, 8.3)	-	8.75 (s, 1H) 8.72 (s, 1H)	7.3-7.4(m, 5H)	1.72-1.84 (m, 2H), 2.44-2.61(m, 4H), 3.37-3.49 (m, 2H)	
6.6h	8.05 (d, 8.3)	7.50 (t, 7.0)	7.38 (t, 7.4)	7.84 (d, 8.4)	-	7.10 (d, 11.0, 1H)	3.44-3.52 (m, 1H), 0.89 (d, 6.6, 3H), 1.14 (d, 6.4, 3H)	1.53-1.78 (m, 4H), 2.32-2.58 (m, 2H), 3.14-3.32 (m, 2H)	
6.6i	8.06 (d, 8.3)	7.39 (t, 8.2)	7.51 (t, 7.5)	7.79 (d, 8.3)	-	6.99 (d, 11.0, 1H)	3.15-3.30 (m, 1H), 0.95 (d, 6.3, 3H), 1.13 (d, 6.8, 3H)	0.15-0.28 (m, 1H), 1.24-1.29 (m, 1H), 1.4-1.7 (m, 4H), 2.57 (dd, 6.6, 7.9, 2H), 3.46 (dd, 15.1, 9.8, 1H), 3.62 (dd, 15.2, 5.3, 1H),	
6.6j	8.02-8.08[c]	7.45-7.52[c]	7.45-7.52[c]	8.02-8.08[c]	-	6.39 (s, 2H)	-	3.03 (s, 3H)	7.39-7.40 (m, 5H)

a) Mixture of 1- and 2-benzotriazolyl isomers in a 1:3 ratio. *b)* Benzotriazole signals of 2-benzotriazolyl isomers: **6.5a**:7.83-7.87 (m, 2H), 7.30-7.36 (m, 2H); **6.5b**: 7.83-7.86 (m, 2H), 7.30-7.37 (m, 2H); **6.6g**: 7.89-7.92 (m, 2H), 7.29-7.24 (m, 2H). *c)* Overlapped signals. *d)* Mixture of 1- and 2-benzotriazolyl isomers in a 1:2 ratio. *e)* Mixture of 1- and 2-benzotriazolyl isomers in a 3:1 ratio.

usually molten during refluxing. Two phases, the organic mixture and performance fluid, were present throughout the duration of the reaction.

All reactions were monitored by the quantity of water distilled. Upon completion of the reaction, solid products were obtained by simple filtration. The performance fluid was washed with methanol to remove contaminants before reuse.

Preparation of Adducts **6.5** from Amines. When benzotriazole, aldehyde and primary or secondary aromatic amine were refluxed in performance fluid under reversed Dean-Stark conditions, benzotriazole derivatives **6.5a-b** were obtained quantitatively as a mixture of the 1- and 2-benzotriazolyl isomers, with the 2-benzotriazolyl isomer predominating. When volatile isobutyraldehyde was used (for the preparation of **6.5b**), the reaction did not occur instantaneously. Refluxing for one or two hours was required to establish equilibrium before the reversed Dean-Stark trap was attached. When this initial reflux was not performed, some of the unreacted isobutyraldehyde was removed leading to an incomplete reaction. An alternative was to use an excess of the volatile isobutyraldehyde to convert the less volatile benzotriazole and *p*-methylaniline into the product **6.5b**.

Preparation of Adducts **6.6** from Amides. Benzotriazole adducts **6.6d-f** were synthesized similarly from 2-pyrrolidinone, benzotriazole and the appropriate aldehyde in excellent yields. 1-Hydroxymethyl-1*H*-benzotriazole, readily available from benzotriazole and aqueous formaldehyde solution [52JA3868], was used in the preparation of adducts **6.6b-c, f** and **j**. Reactions of amides other than 2-pyrrolidinone were slower and a catalytic amount of an acidic resin was required. However, we found that benzamide, 4-methylbenzamide, urea and *N*-methylbenzamide gave the desired products **6.6a-c** and **6.6j** in excellent yields, without the need for further purification. The solid products were conveniently collected by simple filtration. Further purification was necessary when 2-piperidone and ε-caprolactam were reacted with the appropriate aldehyde to give adducts **6.6g-i.** The examples in Table 6.1 demonstrate the versatility of the procedure: aliphatic and aromatic aldehydes, primary and secondary amides, and urea all gave equally high

yields. Most yields of **6.6** are significantly higher than those obtained by the comparable preparations in either AcOH or a normal Dean-Stark apparatus with benzene or toluene, e.g. 97% for **6.6a** and 80% for **6.6j** vs. 24% [91JOC4439] and 48% [93JOC2086], respectively. The reactions in performance fluids are faster than those carried out in benzene or toluene with a normal Dean-Stark trap as demonstrated by the uncatalyzed reactions of 2-pyrrolidinone with benzotriazole and aldehydes. This is probably due to the higher concentration i.e. in performance fluid, the reaction proceeds as in the absence of solvent.

6.3 Synthesis of *N*-[2-(Benzotriazolyl)ethyl]-*N*-methylformamide

2-(1-Benzotriazolyl)-3-methyloxazolidine **6.7** was regarded as a versatile building-block in organic synthesis. In this laboratory, compound **6.8** was readily available from triethyl orthoformate and benzotriazole, using performance fluid methodology (Figure 6.3).

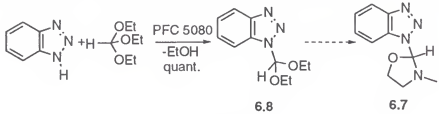
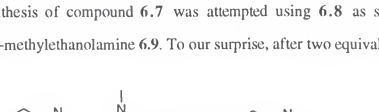


Figure 6.3

The synthesis of compound **6.7** was attempted using **6.8** as starting material together with *N*-methylethanolamine **6.9**. To our surprise, after two equivalents of



Scheme 6.4

ethanol were removed from the reaction mixture, compound **6.10** was isolated in 82% yield as a mixture 1:1.6 of benzotriazol-2-yl and benzotriazol-1-yl derivatives, respectively.

The possible mechanism is a good example of how a good leaving group and a powerful alcohol removing agent can act in a synergetic manner and drive the equilibrium (Figure 6.5). The resulting ion pair **6.11** has two rational transformation pathways shown in Figure 6.6.

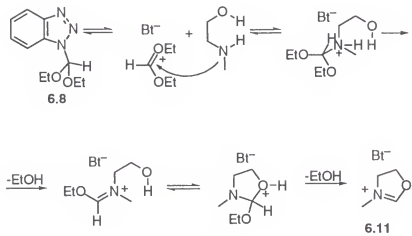


Figure 6.5

The fact that path (a) is favored over path (b), is in agreement with the principle of thermodynamic stability, the formation of an amido group being more favorable than formation of a five membered ring. When considering the ion pair **6.11**, one can write **6.12** and **6.13** as resonance structures for the carbocation where the positive charge is

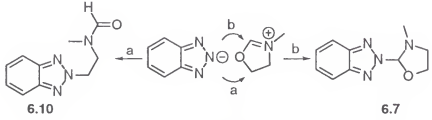


Figure 6.6

more likely to be accomodated by the nitrogen rather than by the oxygen. By replacing the oxygen with sulfur, the contribution of the resonance structure **6.13** would be more important and the behavior of this cation towards nucleophiles might be changed.

6.12 **6.13**

In summary, a method for the synthesis of β–benzotriazolylformamides has been developed by making use of the adduct of benzotriazole and triethyl orthoformate, and *N*-methylethanolamine and the powerful ethanol removing ability of perfluorocarbon fluids.

6.4 Conclusions

Performance fluids provide a new organic reaction medium which has several advantages for the preparation of benzotriazole derivatives: i) the reactions are faster and the yields are higher than reported in previous methods; ii) the reactions are more convenient to work up; iii) performance fluids, when used in conjunction with a reversed Dean-Stark trap, provide a new type of water-removal system; iv) performance fluids can be reused. These features presumably extend to other organic reactions in performance fluids and therefore, are of potential industrial interest.

6.5 Experimental Section

General Methods. Proton and carbon NMR spectra were run on a Varian VXR300 instrument at 300 and 75 MHz, respectively, with tetramethylsilane as the internal standard. Deuterochloroform was used as a solvent unless otherwise specified. Melting points were determined on a hot-stage apparatus. Elemental analyses were run on a Carlo Erba 1106 elemental analyzer.

General Procedure for the Preparation of Benzotriazole Derivatives **6.5a-b.**

A mixture of benzotriazole (1.19 g, 10 mmol), aldehyde (10 mmol), amine (10 mmol) and strongly acidic cationic resin Amberlyst®15 (0.1g) was heated under reflux together with 5 mL of performance fluid (available from 3M Co.) in a 50 mL round bottom

flask fitted with a reverse Dean-Stark device. After refluxing for the appropriate time (Table 6.1), water (0.2 mL) was removed from the trap. The mixture was allowed to cool and the solid was separated from the performance fluid by filtration. The product was dissolved in benzene (100 mL), the resin filtered off and the solvent removed to give the product.

Table 6.4. Elemental Analyses for the Novel Benzotriazole Derivatives **5a-b** and **6b-e**, **g-i**

	Found %			Calculated %		
Cpd	C	H	N	C	H	N
6.5a	71.85	5.07	23.38	71.74	5.02	23.24
6.5b	72.52	7.19	19.87	72.83	7.19	19.98
6.6b	67.71	5.31	21.14	67.65	5.30	21.04
6.6c	49.98	4.82	36.89	50.26	4.74	36.63
6.6d	69.47	5.57	19.37	69.85	5.52	19.16
6.6e	64.88	7.05	21.81	65.09	7.02	21.69
6.6g	70.46	5.90	18.50	70.57	5.92	18.29
6.6h	66.17	7.46	20.76	66.15	7.40	20.57
6.6i	66.90	7.76	19.68	67.11	7.74	19.56

General Procedure for the Preparation of Benzotriazole Derivatives **6.6a-j**.

A mixture of benzotriazole (1.19g, 10 mmol), aldehyde (10 mmol), amide (10 mmol) and strongly acidic cationic resin Amberlyst®15 (0.1g) was heated under reflux together with 5 mL of performance fluid (available from 3M Co.) in a 50 mL round bottom flask fitted with a reverse Dean-Stark device (the synthesis of adducts **6.6b-c, f** and **j** was carried out using 1-hydroxymethyl-1*H*-benzotriazole (1.49g, 10 mmol) in place of benzotriazole and formaldehyde). After refluxing for the appropriate time (Table 6.1), water (0.2 mL) was removed from the trap. The mixture was allowed to cool and the solid was separated from the performance fluid by filtration. The product was dissolved in chloroform (100 mL), the resin filtered off and the solvent removed to give the product. The adducts **6.6g-i** were recrystallized from hexane: EtOAc = 1:1.

Preparation of (Benzotriazol-1-yl)diethoxymethane **6.8**

This compound was prepared according to the published literature procedure [97JOC700].

Preparation of *N*-[2-(1*H*-benzotriazol-1-yl)ethyl]-*N*-methyl-formamide and *N*-[2-(2*H*-benzotriazol-2-yl)ethyl]-*N*-methyl-formamide **6.10**

(1*H*-Benzotriazol-1-yl)diethoxymethane **6.8** (4.42g, 0.02 mol), *N*-methyl ethanolamine (1.50g, 0.02 mol) and PFC 5080 (bp 104 °C) were refluxed with a reversed Dean-Stark for 2h. The floating oil was separated from the PFC 5080 and was subjected to column chromatography on silica gel with ethanol:ethyl acetate = 1:9. The first fraction (R_f = 0.37) was the benzotriazol-2-yl isomer: yield 1.27 g colorless prisms (31%), mp 77.5–78.0 °C. ^{1}H NMR δ (1:1 mixture of rotamers) 2.64[2.91] (s, 3H), 3.96–4.04 (m, 2H), 4.88–4.95 (m, 2H), 7.37–7.41 (m, 2H), 7.72[8.02] (s, 1H), 7.82–7.88 (m, 2H); ^{13}C NMR δ (1:1 mixture of rotamers) 29.3[35.2], 44.7[49.0], 53.6[53.8], 117.9, 126.5[126.7], 144.4[144.4], 162.4[162.8]. Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found C, 59.09; H, 5.98; N, 27.63. The second fraction (R_f = 0.27) was the benzotriazol-1-yl isomer: yield 2.08 g colorless prisms (51%), mp 86.0–86.5 °C. ^{1}H NMR δ (2:1 mixture of rotamers) 2.66[2.89] (s, 3H), 3.87–3.93 (m, 2H), 4.80–4.89 (m, 2H), 7.36–7.41 (m, 1H), 7.48–7.54 (m, 1H), 7.59–7.62 (m, 1H), 7.66[7.99] (s, 1H), 8.04–8.07 (m, 1H); ^{13}C NMR δ (2:1 mixture of rotamers) 35.4 [29.7], 44.8[44.6], 48.6[45.6], 109.0[108.4], 119.7[120.1], 124.0[124.1], 127.6[127.8], 133.1[132.8], 145.6, 162.9[162.2]. Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found C, 58.61; H, 5.92; N, 27.83.

CHAPTER 7
CONCLUSIONS

A study of a variety of carbon–carbon bond forming reactions has been caried out which utilizes benzotriazole as an efficient synthetic auxiliary. These reactions include regiospecific insertion of aryl- and heteroaryl-bearing carbon, homologation of aldehydes and ketones to the corresponding carboxylic acids, nucleophilic substitution of hydrogen in nitroarenes with carbon nucleophiles, and α-aryl-alkenylation of a variety of aldehydes, oxiranes, alkyl halides, isocyanates and acyl chlorides.

Substituent effects on the relative migration rates were investigated in the insertion reactions of 1-(4-methoxybenzyl)benzotriazole with benzophenones. The small and negative Hammett ρ^+ value (-0.92) suggested that the rearrangements proceed *via* early, reagent-like, electron deficient transition states.

The vicinal elimination of silicon from 2-benzotriazolylethylsilanes provides a versatile method for the introduction of 1-arylethenyl moieties into organic molecules. The vicinal elimination of silicon can be accomplished by several protocols including: pyrolysis, [1,4]-Brook rearrangement, and fluoride ion induced β-elimination.

A general regiospecific method for the synthesis of *p*-nitroaryl-diarylmethanes has been developed starting from diarylmethanols and 2- and/or 3- substituted nitrobenzenes *via* vicarious nucleophilic substitution (VNS) of hydrogen. In these cases, VNS complements Friedel-Crafts reactions for the synthesis of triarylmethanes. Oxidative nucleophilic substitution of hydrogen which is observed as a side process during VNS, is utilized for the synthesis of 4-nitrobenzophenones.

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The reference citation system employed throughout this dissertation is that from "Comprehensive Heterocyclic Chemistry II" (vol. 1) Pergamon Press, 1996 (Eds. Katritzky, A. R.; Rees, C. W. and Scriven, E.).

Each time a reference is cited, a number and letter code appear in brackets, for example [00ABC000]. The first two digits denote the year of the twentieth century, the letter code is an abbreviation for the journal or book cited and the last digits represent the page number. Additional notes to this reference system are as follows:

(ii) References are listed consecutively by year, alphabetically by the journal code and then by page number.

(ii) Each reference code is followed by the conventional literature citation complete with the name of the authors.

(iii) Journals which are published in more than one part, or more than one volume per year, include in the abbreviation cited the appropriate part or volume number.

(iv) Books and journals which are less commonly used are called "MI" for miscellaneous.

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BIOGRAPHICAL SKETCH

Dorin Toader was born on January 8, 1961, in Galati, Romania. In 1979, as a high-school student, he represented Romania at the International Chemistry Olympiad where he was awarded the bronze medal. He graduated in 1985 from the Polytechnic University in Bucharest *summa cum laude* with a BS in organic chemical technology. From August 1985 to August 1987 he worked as a process engineer at the VISCOFIL yarn plant in Bucharest during the required industrial training. In August 1987 he joined the Chemical and Pharmaceutical Research Institute in Bucharest. In March 1991, he was conferred the title of scientific researcher.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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